

**BETWEEN SELF AND OTHER:
AN INVESTIGATION INTO THE BEHAVIOURAL AND
NEURAL CORRELATES OF AMBIGUITY IN AGENCY**

Thesis submitted in accordance with the requirements of the University of Liverpool
for the degree of Doctor in Philosophy

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May 2017

Institute of Psychology Health and Society



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ABSTRACT

Between self and other: An investigation into behavioural and neural correlates of ambiguity in agency. By Christophe Emmanuel de Bézenac

Background: In most circumstances we easily distinguish changes to the external world brought about by our own actions from those with external origins. However, there are contexts where the sense of agency is put into question. Little is known about ambiguity characterised by a lack of information for self-other differentiation, despite its relevance to symptoms and levels of consciousness associated with certain mental health conditions. In this PhD thesis by publication, behavioural and neuroimaging methods are used to explore self-other processing capacities in ambiguous conditions. Individual differences are examined in relation to brain response with the aim of shedding light and generating further testable hypotheses on mechanisms of agency in both health and psychosis.

Chapter 2: Building on ideas from developmental and perceptual psychology, Chapter 2 lays out the theoretical framework and rationale behind the experimental work. The paper defines the concept of ambiguity in relation to self-other processing. With caregiver-infant interactions and social interactions more generally described as inherently ambiguous, a key proposal is that experience in ambiguity-promoting settings provide conditions necessary for developing reality-testing abilities and a flexible sense of self-other associated with mental health. Such abilities may be malleable, however, continuing to develop through experience in activities involving intricate joint action such as social dialogue. It is argued that activities such as music-making which require self-other distinctions, yet make differentiation challenging may particularly hone these skills. Implications for phenomena such as hallucinations associated with reduced attributional abilities are discussed.

Chapter 3: In the first experimental study, a task was developed that manipulates ambiguity by controlling the probability that a participant's finger taps results in auditory tones as opposed to tones generated by 'another's finger taps'. The ability to accurately attribute actions to self and to other was negatively related to hallucination proneness (HP) and positively related to musical experience (ME). This pattern of results was accentuated by ambiguous conditions where the probability of self- and other-generated tones was equal. This not only associates HP with specific difficulties in dealing with ambiguity, but also supports the notion that attribution abilities are malleable and can improve through experience in ambiguous settings such as those involving intricate joint action.

Chapter 4: Chapter 4 investigated neural responses to modulating the degree of control belonging to self and other using the probability method tested in Chapter 3 in a parametric fMRI block design. Linear and non-linear stimulus-response functions highlighted a network of brain regions previously associated with motor control and self-other processing to be particularly sensitive to control belonging to self. All regions also displayed significant non-linearity with decreased response in ambiguous conditions. This study provides initial insight into attributional ambiguity-processing in the brain.

Chapter 5: In Chapter 5, neural responses to the task were examined in relation to individual differences. Combining whole-brain univariate and a task-based ICA approach, results showed increased ambiguity-related response in sensory and DMN regions to be related to positive schizotypy and difficulties in processing ambiguity, in contrast to task performance and musical experience which correlated with reduced response.

Chapter 6: The final study examined the effects of attribution performance, including performance specifically related to ambiguity, on resting-state functional connectivity using ICA, dual regression and a network analysis. Findings showed connectivity between frontal networks and other brain regions increased with reduced task performance.

Conclusions: The thesis concludes with a discussion of these collective findings and implications for future research. Together the behavioural and imaging findings point towards the importance of ambiguity in self-other processing. Increased insight into the topic may enhance our understanding of agency mechanisms underlying 'self-disorders' such as schizophrenia and eventually contribute to extending the range of therapeutic possibilities.

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisor Professor Rhiannon Corcoran for seeing the potential in, and helping me develop and hone my research ideas and tolerate and value moments of uncertainty. I also thank my co-supervisor, Dr Vanessa Sluming for her support. Thank you to members of the psychosis and perception labs for contributing to a context that promotes the sharing of concepts and methods, as well as to the MARIARC team, particularly Valerie Adams, for facilitating MRI data collection. I would like to acknowledge Joe Furlong, Oran Quinn McKie, and Fahad Alhazmi for their assistance in gathering data as well as the participants that took part. Particular thanks to Professor Richard Bentall, Dr Marco Bertamini, and Dr Georg Meyer for engaging dialogues, and to Dr Noreen O'Sullivan, Dr Andre Gouws (University of York), and Dr David Clewett (University of Southern California) for their valuable advice at critical periods of the research process. I also want to express my appreciation to the Institute of Psychology Health and Society, University of Liverpool for funding the study. Finally, I am deeply grateful to Dr Rachel Swindells for her unconditional support and encouragement, for the stimulating discussions that have shaped my thinking over the years, and to Mailys Swindells de Bezenac for the wonderful person that she is, for her insatiable curiosity and vitality that provided a continuous reminder about how to be, and explore in the world.

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LIST OF KEY ABBREVIATIONS

ACC	anterior cingulate cortex
Accbns	accumbens
AM	ambiguity-related misattribution
AN	auditory network
AS	auditory streaming
B	baseline
BA	Brodmann area
BOLD	blood oxygen level-dependent
C1-10	conditions 1 to 10
Caud	caudate
CD	cognitive disorganisation
Cerbm	cerebellum
CGa	cingulate gyrus anterior division
CGp	cingulate gyrus posterior division
CO	central opercular cortex
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
E	extremes
fMRI	functional magnetic resonance imaging
FOC	frontal orbital cortex
FP	frontal pole
FWE	familywise error
GLM	general linear model
HP	hallucination proneness
IA	introvertive anhedonia
IC	independent component
ICA	independent component analysis
ICN	intrinsic connectivity networks
ID	individual difference
IN	impulsive nonconformity
INS	insular cortex

IPL	inferior parietal lobe
L	left
l-FPN	left-lateralised frontoparietal network
LSHS-R	Launay-Slade hallucination scale revised
M	middle
ME	musical experience
MPFC	medial prefrontal cortex
O	other
OF	occipital fusiform gyrus
OLi	lateral occipital cortex inferior division
O-LIFE	Oxford–Liverpool inventory of feelings and experiences
OP	overall performance
OP	occipital pole
PCC	posterior cingulate cortex
PE	prediction error
Perf	performance
PET	positron emission tomography
PFC	prefrontal cortex
PO	parietal operculum cortex
POG	postcentral gyrus
PPC	posterior parietal cortex
preSMA	pre supplementary motor area
PRG	precentral gyrus
pSTS	posterior segment of the superior temporal sulcus
Put	putamen
R	right
rFPN	right-lateralised frontoparietal network
rMTG	right middle temporal gyrus
RSN	resting state network
S	self
SMA	supplementary motor area
SMC	supplementary motor Cortex
SMN	sensorimotor network
T	task

Thal	thalamus
ToA	tolerance of ambiguity
TP	temporal pole
TPJ	temporo-parietal junction
UE	unusual experiences
VLPFC	ventrolateral prefrontal cortex
VN	visual network

PREFACE

1. Introduction

In normal circumstances we are able to easily distinguish between changes to the external world brought about by our own actions from those with external causes. However, there are contexts where the causal boundaries of self and other (the sense of agency and body ownership) are thrown into question. Despite the recent flurry of theoretical and empirical investigations into agency, little is known about ambiguous contexts characterised by a lack of information for self-other differentiation; yet ambiguous states are important in relation to symptoms and levels of consciousness that characterise certain mental health conditions. This PhD uses behavioural and neuroimaging methods to explore self-other processing and, in particular, ambiguity in differentiating between action outcomes belonging to self in relation to those belonging to other/s. Individual differences in response to ambiguity are investigated with the aim of generating testable hypotheses about mechanisms of agency in both health and psychosis.

2. Thesis format and outline

This thesis is presented in the alternative format as a series of papers that have either been submitted to, or published in peer-reviewed journals. It should be noted, however, that compared to a traditional thesis format, this document contains a higher degree of repetition/redundancy, given the need for individual journal articles to present a self-contained argument. The document is divided into 6 chapters. Following the preface, Chapter 1 outlines the rationale and theoretical framework behind the experimental investigations. The experimental studies are presented in Chapters 2-5, while Chapter 6 provides a summary and discussion of findings and their implications for future research.

3. Authorship Contributions

All of studies included in this thesis were conceived of designed by Christophe de Bézenac with guidance from supervisors Prof Rhiannon Corcoran and Dr Vanessa Sluming. The author completed data collection, analysis and interpretation, and the writing of associated research papers. Undergraduate student Oran Quinn McKie and postgraduate student Joe Furlong (see acknowledgements in Chapter 4) assisted in data collection. Listed co-author Dr Rachel Swindells provided critical revisions for Chapter 1. Dr Noreen O’Sullivan aided in the design of the behavioural statistical analyses (multi-level modeling) used in Chapter 2. Dr Andre Gouws advised on the parametric fMRI analysis described in Chapter 3 while David Clewett advised on the design of the task-based ICA analysis conducted in Chapter 4.

CHAPTER 1

Ambiguity in self-other processing: a theoretical framework with implications for mental health

[de Bézenac, C. E., Swindells, R., & Corcoran, R. (under review). Ambiguity in self-other processing: a theoretical framework with implications for mental health. *Psychological Review*]

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1.1. Abstract

While distinguishing between the actions and physical boundaries of self and other (non-self) is usually straightforward there are contexts in which such differentiation is challenging. For example, self-other ambiguity may occur when actions of others are similar or complementary to those of the self. Even in the absence of such situational challenges, individuals experiencing hallucinations have difficulties with this distinction, often experiencing thoughts or actions of self as belonging to other agents. This paper explores the role of ambiguity in self-other differentiation with the aim of contributing to a theoretical framework for understanding prerequisites for mental health. A key proposal is that engagement in ambiguous contexts that challenge distinctions between self and other may provide optimal conditions for refining reality-testing skills related to self-other differentiation. With attunement in early caregiver-infant interactions framed as one such context, the argument positions vulnerability to psychosis within a developmental framework. However, as these early-acquired skills are likely to be malleable, they will improve through

practice. Using music-making to illustrate, we postulate that increasing engagement in ambiguous situations such as those involving intricate joint action contributes to the continued development of an adaptive sense of self and other essential to healthy social functioning. Increased insight into the role of ambiguity may enhance our understanding of mechanisms underlying ‘self-disorders’ such as schizophrenia and may eventually extend the range of social and arts-based therapeutic possibilities.

“The brain abhors ambiguity, yet we are curiously attracted to it” Ramachandran & Ramachandran, 2008

1.2. Introduction

Being alive is to possess a boundary or membrane that delimitates the inside from the outside, regulating what is kept in and let out, as well as what is kept out and let in. Awareness of the dynamic relationships that exist between oneself, one’s surroundings and other agents is a primary, on-going task of the perceptual system (Gibson, 1978; Gallagher, 2005; Critchley et al., 2004; Gallese & Sinigaglia, 2011; Damasio, 2012). But how do we do this? When we do things, how do you know that it is ‘us’ as opposed to another that is doing it? In most situations identifying one’s own self as separate from surroundings and other individuals and being able to attribute behaviours and events to their respective sources seems relatively straightforward and an essential part of everyday actions and interactions. However, there are times when this task is challenging, where information for distinguishing self from other (non-self) is either reduced or cannot be identified. While perceptual challenges of this sort have commonly been associated with phenomena such as hallucinations and delusions, self-other ambiguity can also exist as a characteristic of the external environment. Drawing from perceptual and developmental psychology, neuroscience, and psychodynamic theory, we explore the interaction between individual and environmental factors, proposing that ambiguity plays an important role in the development of an adaptive, flexible and coherent sense of self essential to mental health and wellbeing through life.

1.3. Defining the self

The sense of self (and of ‘other selves’), is a perceptual, cognitive, and conceptual organising system by which we encounter the world (e.g., James, 1891; Baumeister & Bushman, 2011; Damasio, 2003; Stern, 1985; Rogers, 1961), which is central to any understanding of human psychology and mental health. Yet still, its conceptualisation remains mired in a theoretical quagmire (Gallagher, 2013; Berrios & Markova, 2003; Klein, 2012; Baumeister, 1987; Guignon, 2004) because sense of self is a complex and multifaceted construct involving over-arching and over-lapping processes like consciousness, agency, memory and social and cultural identity (Leary & Tangney, 2012; Gallagher, 2000; Klein & Gangi, 2010). Typically, however, theoretical accounts share a similar focus on the sensory-motor and mental processes which endow one with feelings of singularity, stability and coherence as an individual human being (Siegal, 2001; Damasio, 2003). A distinction is also commonly made between a ‘minimal’ or ‘core’ self, accessible to immediate self-consciousness as moment-to-moment streams of multisensory, perceptual and affective experience, and a narrative or ‘extended’ self drawing, for example, on higher order mental representations and episodic memory (Gallagher, 2005; Sass & Parnas, 2003; Stern, 1985; Siegel, 2001; Klein & Gangi, 2010). The former – the main focus of the current paper – is an essentially embodied phenomenon encompassing a sense of body (bodily unity/coherence,) ownership and agency, which, crucially, allows the differentiation of self from other/environment. The latter encompasses a sense of self-identity and personhood often over a longer time-frame (Gallagher, 2013). Though discrete phenomena, theorists have emphasised the interdependency between these lower and higher order configurations, with multiple layers of self regarded as operating in parallel throughout life. For Stern (1985), for example, the achievement of a ‘core self’ between two to seven months of age not only sets the ground work for the subsequent emergence of ‘verbal’ and ‘narrative’ selves, but also establishes a sense of one’s self as a unified and integrated but separate being. Thus, this functioning core self is essential for maintaining mental health across the lifespan, keeping at bay feelings such as dissociation and fragmentation (Fink, 1988).

Aside from the identification of different types of self (Klein, 2012), researchers

across domains have emphasised the inherent malleability of these differing ‘selves’. Anthropologists argue that definitions of self are, at least in part, culturally determined and vary across time and place, where sense of self is regarded as more or less fluid in distinct socio-cultural contexts (Christopher & Hickenbottom, 2008; Benning, 2013; Baumeister, 1987; Guignon, 2004). Childhood researchers likewise highlight how the emergence of a sense of self across developmental milestones and in tandem with wider developmental achievements occurs in transaction with necessary environmental inputs. While not denying the influence of genetic inheritance, the neurological/biological basis of one’s sense of self is shaped to a large extent through interactions in the infant’s social environment and interpersonal relationships (Damasio, 1999; Siegal, 2001; Schore, 2015, 2003; Tronick, 2007).

1.4. Physical and agentic boundaries of self and other

From the very start of life, we learn that there are fundamental differences between the outcomes of our own actions and the outcomes that results from the behaviour of others around us (see White 1995:50-56); we come to experience direct control over our actions and an ability to move and manipulate objects, surfaces and even, eventually and to a certain extent, the actions and thoughts of other agents (Gibson and Pick 2000:160). This experience relies on knowing the boundaries of entities, where one thing ends and another begins. But how are such boundaries determined, particularly those that exist between self and other agents? Put in more concrete terms, how can sensory signals deriving from the presence or movements of one entity be disentangled from those belonging to another?

It has been argued that we do this by relying on invariants – gestalt-like regularities about the characteristics of animate and inanimate objects (Stern 1985; Palmer, 2003; Bregman, 1994; Gibson, 1966). For example, an object tends to possess unity: its parts move together when they move or are moved. The stimuli generated by such movement, whether picked up in the form of sound, light, taste, or pressure, are therefore likely to seem coherent and perceived as belonging together (Rock & Palmer, 1990). The sounds of a person speaking, for instance, derive from a similar location and change together gradually rather than suddenly, sharing a common

temporal and intensity structure. Sounds that do not share this coherence, such as an utterance that is suddenly much louder or derives from a different location, suggest the presence of another speaker. Therefore, while coherence is the norm (an invariant) within entities, incoherence is expected between them and is therefore used to mark their distinction. Separate entities segregate by virtue of their distinctness: they occupy different locations to other nearby objects and surfaces and tend to move independently, generating stimuli with temporal and intensity profiles that are incoherent in relation to one another.

As the above examples indicate, the boundaries of entities and, in particular, those of animate entities are determined by how stimulus features such as intensity, timing and shape vary over time (Stern, 2010). Stimuli with matching profiles are perceived as belonging together and having derived from a coherent entity (see Fig. 1.1). As Stern argues (1985:154), such dynamic features are amodal in the sense that they describe variation in signals picked up in all sensory modalities, including those originating from within the body (also see Stein & Meredith, 1993; Deneve & Pouget, 2004; Pascual-Leone & Hamilton, 2001; Lewkowicz & Turkewitz, 1980; Kuhl & Meltzoff, 1982). For example, a sudden increase of intensity does not only refer to changes in aspects of sound, light, touch and smell, but also to variation in more covert signals such as proprioceptive feedback or an affective sensation such as fear. Significant to agency, it can also describe the content of sensorimotor as well as longer-term predictions that one forms about the results of actions as they unfold over time.

Coherence between stimuli originating outside and inside the body provides essential information about which entity corresponds to self as opposed to other, contributing to the feeling of self-agency, the sense that “I am the source of my thoughts and actions” (Gallagher, 2000). This derives in part from basic physiological systems of the body in relation to sensory stimuli (Poulet & Hedwig, 2007; Jeannerod, 2003; Von Holst, 1954). As the ‘comparator model’ suggests, events that match the predicted consequences of action are experienced as belonging to self (prediction error is small), while mismatch (or large prediction error) is attributed to an external cause (Wolpert & Miall, 1996; Frith, Blakemore, & Wolpert, 2000; Trinity & Sommer, 2008; Gandevia & Burke, 1992). In other words, an invariant of agency is

that the difference between predicted variation in the intensity, timing, and shape of an action and the actual intensity, timing, and shape of the resulting stimuli is likely to be small when that action belongs to self, compared to when it belongs to another individual. Stimuli belonging to self as opposed to another agent are likely to vary with a number of other covert (internally-derived) signals not directly accessible to other individuals. The latter could include signals that precede, accompany or follow actions, such as volition (as well as higher-order intentions and goals), action prediction, sensory and proprioceptive feedback, affective sensation, as well as the evaluation of past behaviour (Gallagher, 2000; Stern, 1985; Wegner, 2002; Wegner & Sparrow, 2004).

1.5. Ambiguity between self-other boundaries

In most situations, stimulus features either vary coherently or incoherently in relation to one or more entities, with available sensory modalities pointing in the same direction. This enables boundaries that exist between entities including self and other and the control that these have over occurrences to be clearly defined. However, rather than seen as binary opposites, there is evidence that coherence and incoherence are better conceptualised as opposite ends of a continuum (Farrer et al., 2003). With effort, an agent can generate stimuli that are partially incoherent, adopting a characteristic more commonly associated with a number of unrelated objects or agents. A ventriloquist, for example, rapidly changes the quality of her/his voice to promote the illusion of being in the presence of more than one individual (Soto-Faraco et al., 2002; Alais & Burr, 2004; Howard, & Templeton, 1966). Autonomous agents can also act with partial coherence in relation to one another, generating stimuli that vary with a degree of synchrony more typical of a single agent, such as a group of individuals marching together (McNeill, 1995).

Furthermore, actions belonging to self can display a degree of incoherence between internal signals such as action predictions and external feedback: consider the experience of using a malfunctioning computer mouse where visual feedback does not correspond to intended and performed actions. Experiments set up to investigate mechanisms of agency typically introduce spatial or temporal distortions to the

outcome of a participant's actions to manipulate the authorship that a person feels over that action (Farrer & Franck, 2007; Blakemore et al., 2000; Franck et al., 2001; Sato & Yasuda, 2005). As action-outcome discordance increases (e.g., using delay or spatial displacement), the participant is more likely to disown the sensory feedback, attributing it instead to an external cause. The opposite is also possible. Signals related to actions of self, including intentions, predictions, proprioception and affective sensation, can be coherent with externally generated stimuli. This is demonstrated by Wegner and Sparrow (1999) who found that having thoughts that happened to be coherent with an action performed by the experimenter made participants more likely to experience ownership over that action – a phenomena that they called vicarious agency.

Invariants can, therefore, be weakened. In summary, although it is the case that changes in intensity, timing and shape are expected to be coherent within but not between entities, and interoceptive-exteroceptive coherence is the norm for self-generated but not for externally-generated actions, such regularities can be partially violated. This can result in the emergence of conflicting groupings, with some features pointing towards illusory boundaries or causal relationships and others specifying 'reality' – the actual boundaries or causal relationships that exist in the world. Informational conflicts may cause us to momentarily misperceive stimuli deriving from multiple agents as belonging to a single coherent agent (e.g., the marching group) or, vice versa, stimuli from a single agent as belonging to multiple agents (e.g., the ventriloquist). In relation to agency, we may also feel that our own thoughts, emotions, and actions and their consequences belong to another individuals. The ouija board game exemplifies the latter: the combined force that a number of participants exert on the centrepiece makes individual contributions difficult to ascertain, promoting the misattribution of movement to an external force (under-attribution to self) (Ansfield and Wegner, 1996). Conversely, the illusory experience of controlling externally caused events can also occur (over-attribution to self). One example is a conductor who experiences a high degree of coherence between his/her actions (and associated internal signals such as volition and sensorimotor predictions) and the sensory outcomes of orchestra members' collective actions (Epstein, 1987). However, given that invariants can never be completely violated, such misperceptions are fleeting and rarely complete. Even in controlled

settings where there is an explicit attempt to promote misperceptions, there is generally always sensory information available that continues to point towards the state of the world as it is (Gibson, 1966; 1979).

Ambiguity emerges when invariants are weakened to an extent that multiple conflicting groupings are perceivable, whether these are actual or illusory entity boundaries or causal relationships (see Ernst and Bühlhoff, 2004; Roach et al., 2006). In such contexts, there is insufficient information available to determine which alternative is preferred due to a balance between coherence and incoherence specified by dynamic features of stimuli across sensory modalities (see Rimmon 1977:17). The perceiver is driven to explain or find meaning in the experience. They conduct a series of overt and covert reality tests when faced with inadequate or conflicting information, such as head movements or attention shifts, to search for “information that will reinforce one or the other alternative” (Gibson 1966:303–304). As Ramachadran and Ramachandran (2008) contend, “the brain abhors ambiguity, yet we are curiously attracted to it” – an attraction which may have evolved due to the need for organisms to have an incentive to uncover objects, such as predators, from complex environments (Ramachandran & Hirstein, 1999). Where disambiguating information is limited, the perceptual process is necessarily prolonged, as exemplified by the incessant alternation between the possible alternatives that characterise the viewing of bistable images (e.g., duck or rabbit) (Wernery, 2013). Ambiguity in effect disrupts habitual perception and subjective experience – one is compelled to look and listen again (Rose, 2004:148-149). Artists, writers and performers have long understood and exploited this (Rimmon, 1977:229). Gibson (1979:44) explains that picture-makers enhance aesthetic experience by introducing “a discrepancy of information, an equivocation or contradiction in the same display”, whilst restricting the amount of additional information that can be gathered through objective scrutiny.

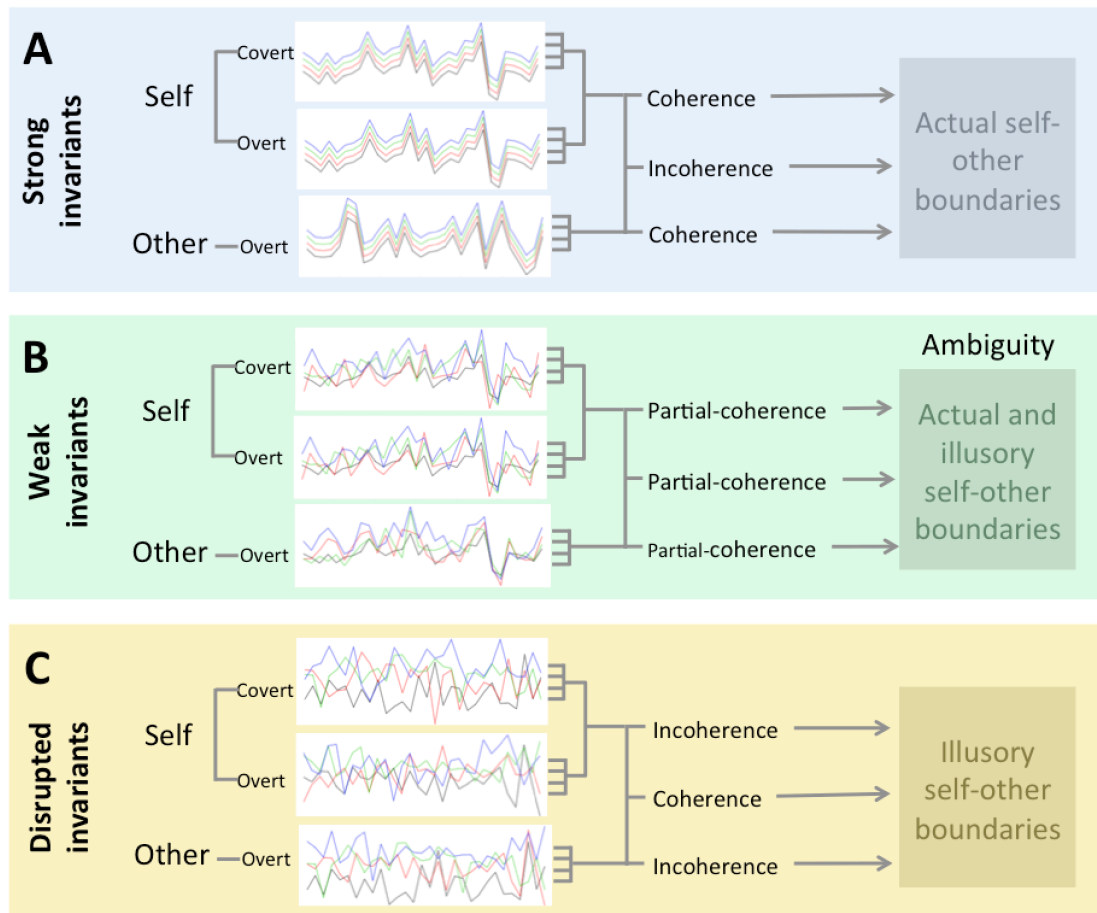


Fig. 1.1. Defining ambiguity between self and other boundaries. Time-series represent sensory signals/stimuli (lines). These signals can either be overt (externally accessible, e.g., sound; vision, smell) or covert (inner-body signals accessible to self, e.g., proprioception, volition, action prediction, emotion sensations). All signals can vary in multiple ways, e.g., modulating in intensity, timing, shape, location and form over time. Coherence between such signals within entities (e.g., self) and incoherence between entities (self and other) is the default (invariant) and allows us to easily perceive the world as it is, i.e., the actual physical and agentic boundaries that exist between entities (A). Invariant can be disrupted: incoherence within and coherence between entities, resulting in illusory boundaries (C). Ambiguity (B) emerges when invariants are weakened to the extent that signals are partially coherent/incoherent within and/or between entities. Both actual and illusory boundaries (physical and agentic) are available for perception and the perceiver can switch between these alternatives.

1.6. Ambiguity and the developing self

Ambiguity in the perception of entity boundaries, particularly relating to self and other, is a pervasive feature in accounts of infantile experience and early processes of separation, individuation and sensory integration. Although rudimentary processes of self-other differentiation including self-agency are commonly thought to be evident from birth (Rochat, 2003; Meltzoff & Moore, 1995), it is generally accepted that an infant's sense of self emerges at psychological and neurobiological levels through its

relationships with others (Damasio, 1999; Siegal, 2001; Bowlby, 1973; Perry, 2002; Tronick, 2007; Schore, 2015). This is supported by evidence for shared neural networks for processing self and other in multiple brain areas including cortical midline, frontal and parietal structures (reviewed in Lieberman, 2007; Uddin et al., 2007; Frith, 2007).

Following the physical separation that begins from the first moments of post-natal life, the human baby is primed to respond to and attract the social contact required for its survival and development (Siegal, 2001; 2010; Schore 2015; 2003; Tronick, 2007; Stern, 1985). The caregiver's first role is not only to provide physiological protection and nourishment but also emotional containment and feelings of self-coherence by regulating his or her changing levels of arousal associated with internally and externally derived sensations. Responding to fluctuating sensorimotor and affective cues, the caregiver seeks, for example, to calm a distressed or over-excitable infant, entertain a passive infant, and temporarily withdraw when an infant is overstimulated, while also attributing intent and agency to such covert behaviours (Brazleton, Koslowski & Main, 1974; Fonagy, 2003; Gergely et al., 2002). Ensuring the infant enjoys sufficient periods of calm to engage in self-perception-based exploratory play also contributes to the early sense of self by means of "the intermodal calibration of the body" (Rochat, 1998).

Drawing on micro-observational studies examining infant-caregiver interactions on a moment-to-moment basis, Stern's work (1985) emphasises the importance of attunement processes, achieved as the caregiver matches to or mirrors the dynamic features of behaviours, particularly those expressing variation in an infant's internal affective states. By minimising the separateness that typically exists between entities, caregivers intuitively seeking to reduce a younger baby's potential frustrations and distress allow the infant to experience an illusion of oneness and pleasurable feelings of agency and extended control over surroundings (Winnicott, 1971; 1960; Fosha, 2001; Glover, 2009; Dowds, 2014; Gergely & Watson, 1996). An example of this is a parent who attunes to the intensity, timing and shape of a baby's animated movements (e.g. raised and lowered arms) by means of accompanying vocalisations (e.g. "wheee!") matching the rise, fall and overall excitation levels inherent in the infant's gestures.

As this scenario exemplifies, empirical work suggests that rather than solely imitating the infant's behaviour, the caregiver, over time, begins to translate the contours of that behaviour into an alternative sensory modality (Crown et al., 2002; Beebe et al., 2010; Jonsson et al., 2001). In perceptual terms, this transformation not only emphasises the dynamic features of behaviour (given that these remain the same), but also provides the infant with opportunities to learn to weigh up and synthesise information from differing modalities that specify internal and external states. That dynamic features are matched in one modality but not another functions to educate attention and help promote sensory integration – the development of a normal sense of self depends on emerging abilities to integrate multisensory input (Postmes et al., 2014). According to Stern (1985), however, it does much more than this in that it also helps the infant to grasp that the caregiver is not only able to mimic his or her literal behaviour, but has understood the affective sensations underlying it. Ultimately, this conveys to the infant that external actions but also internal subjective states of mind in the self and other can be known and shared – an important step in the acquisition of what has variously been called a mentalizing capacity (Frith & Frith, 2006; Fonagy, Gergely & Jurist, 2004), theory of mind and empathy (Premack & Woodruff, 1978; Corcoran, Mercer & Frith, 1995; Baron-Cohen, 1991).

Given that some aspects of behaviour are attuned to, while others are not, and that dynamic features may be matched in one modality but not another, there will always be sensory information continuing to point to the caregiver-infant as separate, distinct entities. With reference to the illustration of cross-modal attunement above, while coherence or 'oneness' is specified in the correspondence between the infant's motions and caregiver's sounds, there is a mismatch between the agents' arm movements which make conflicting cues available to the infant. The fact is there is no such thing as a perfect attunement with a degree of incoherence always pointing towards to divergences between infant and caregiver as distinct agents. Indeed, moments of misattunement, whether purposeful or unintentional (the over or under shooting of behaviour contours), are as necessary as episodes of attunement to help the growing infant identify and integrate the invariants that distinguish its experience of itself from an other as an embodied, feeling and, eventually, thinking being (Stern, 1985; Tronick, 2007; Fonagy & Target, 1996). As clinicians and researchers have

noted, too much, as well as too little attunement coherence are both detrimental to developmental outcomes in this regard (Fonagy, 2003; Jaffe et al., 2001; Stern, 1985). There may be a critical tipping point that is key to life chances and outcomes between enough, not enough and too much attunement.

The overall implicit goal is healthy ambiguity: a balance emerges over shorter and/or longer periods of time in the fluctuation of attunement/misattunement, between stimuli pointing towards caregiver-infant togetherness (coherence) and separateness (incoherence). In the ‘wider-world’ situations that do not allow self and its outcomes to be distinguished from surroundings can be dangerous and perceived as such. The infant’s gradual awareness of his/her separateness and agentic limits (the reality of self/other bounds) is likely to rouse unpleasant feelings associated with helplessness and dependency. The sensitive caregiver responds by creating a safe yet sufficiently motivating context in which the infant is invited to explore and *play* with the boundaries between self and other and, at the same time, his or her own internal and external experiences. While the precise manner in which the caregiver facilitates such implicit learning varies across development, perceptual play in a variety of forms continues to promote awareness of self-other boundaries by bridging the subjective world of the imagination and the outer world of people and things (Winnicott, 1971; Milner, 2010). Being continuously called upon to compare fluctuations in the degree of coherence that exists between entity boundaries and internally and externally derived signals provides the individual with optimal conditions for honing the perceptual, social and cognitive competencies required for a functioning sense of self and of agency. As Winnicott, Milner, Segal and others contend (see Glover, 2009), this in-between space is also the basis of creativity and a capacity to symbolise (to be non-literal or pretend) in the context of verbal thinking and communication with others. In contrast to persisting romantic notions of creativity as the cathartic endeavour of a lone genius, these authors argue that it emerges not by losing touch with reality or with others, retreating into one’s inner world, but instead by an increasingly refined awareness of, and playful engagement with the boundaries between internal and external experience – through a fluid interplay between the two.

1.7. Implications for mental health

Closely allied to this facility to differentiate self and other is an ability to distinguish between what is real from what is imagined, made up or simulated (Fonagy, 2003; Sutton-Smith, 1997). Ecological psychologists contend that the perception of the tangible, external world is always distinguishable from that of mental life such as dreams and hallucination, in that the latter does not yield additional information when subject to scrutiny or ‘reality testing’ (e.g., scanning with eye, head, hand and body movements). Gibson (1970) argues that the reason individuals experience hallucinations or ‘psychedelic experiences’ as external reality reflects either an inability or disinclination to apply the necessary perceptual tests, for example, when under the influence of drugs or during periods of psychological distress. This is supported by theoretical models that understand psychosis as a deficiency in information processing (Aleman, 2014; Bellack et al., 1990; Savla et al., 2012; Green & Horan, 2010) or impaired salience assignment also associated with hyperdopaminergic neural state (Kapur, 2003; Winton-Brown et al., 2014). Though, conflicting cues in the environment are what motivates the search for additional information, ambiguity can stimulate anxiety, impacting on the efficiency and conclusions of ongoing thinking as well as the capacity to apply appropriate reality tests when required (Maule, Hockey, & Bdzola, 2000; Beck & Clark, 1997; Eysenck & Calvo, 1992). One result can be a tendency to over-rely on biases or prior knowledge that no longer apply (Corcoran et al., 2006; Bennett and Corcoran, 2010), with an urge to adopt new certainties too quickly, before a new pattern has had the chance to emerge (Bion, 1970: 124). Notably, an inability to tolerate ambiguity and a proclivity to jump to conclusions in uncertain contexts has been consistently linked to psychopathological disorders including psychosis (Garety et al., 2011; Budner, 1962; Colbert & Peters, 2002; Grube, 2002; Broome et al., 2007; Linney, Peters, & Ayton, 1998; Van Dael et al., 2006).

Early experience in a safe environment that allows actual and illusory boundaries to be evaluated and compared one with the other without confusing the two, develops the ability and propensity to conduct appropriate reality tests on the corporeal and agentic boundaries of self and other. The ambiguous play facilitated by the caregiver enables the infant to experiences different states of self and other over time, leading

to a sense of self that is more resilient and adaptive to the internal and external changes that occur throughout life. By contrast, situations where reality is always or never clear-cut, where invariants specifying entity or agency boundaries remain unchallenged and rarely come into conflict, are not likely to afford such opportunities for psycho-social development. Fonagy (2003) contends that the most crucial outcome of a secure attachment relationship in childhood is the ability to distinguish between and realistically appraise self and other, rather than the usually cited engendered feelings of safety and self-confidence per se. Individuals who do not acquire the competencies required to maintain a distinction between representations of self and other – where the actions and/or feelings of one are habitually confused and misattributed to the other – may have to develop less adaptive strategies to amplify the differences between the two, through for example forms of social withdrawal or preoccupation with other. More generally, all mental illness may be viewed as the mind misinterpreting its own experience of itself and of other (Fonagy & Campbell, 2015), with a failure to establish developmentally appropriate constructs of self in the early years implicated in the aetiology of various disorders (Fink, 1988; Kyrios, 2015). This is particularly apparent in agency-related phenomena such as hallucinations and delusions of control thought to be rooted in difficulties in differentiating between thoughts, intentions and actions belonging to self from those belonging to others (Sass & Parnas, 2003; Bentall et al., 2007; Spence et al., 1997; Parnas & Handest, 2003; Jeannerod, 2009; Ditman & Kuperberg, 2005; Lindner et al., 2005; Frith, 2005; Woodruff, 2004).

Behavioural and neuroimaging research has begun to shed additional light on mechanisms underlying the sense of self and of agency (Sperduti et al., 2011; Nahab et al., 2011; David, Newen, & Vogeley, 2008) and on the impact of development on such processes (e.g., Kircher & David, 2003). Early attachment experiences can positively or negatively shape genetically primed neural structures that underpin perceptual and cognitive organisation of self (Siegal, 2001; Bowlby, 1973; 1982, Schore, 2015, 2003; Tronick, 2007). For example, a body of research has focused on experience-dependent maturation and stabilisation of interconnections between the orbitofrontal cortex with cortical and sub-cortical areas in early life, and the essential role these associated pathways play in self-regulatory behaviour and self-monitoring (reviewed in Schore, 2015). Likewise, a number of studies have shown that

disrupting parent-infant interactions during early development can have significant impact on the development of the prefrontal cortex in humans and other mammals (reviewed in Kolb et al., 2012). This region, which has been associated with guiding motor, affective, cognitive, and social behaviour over time (Wood & Grafman, 2003; Mitchell, Banaji, & MacRae, 2005), is thought to have a prolonged, experience-dependent development, making it particularly susceptible to abnormal functioning as expressed in multiple neuropsychiatric disorders (Braun & Bock, 2011; Stuss, Gallup, & Alexander, 2001; Tekin & Cummings, 2002).

While the development of a core sense of self/other in infancy is a specific keystone achievement associated with critical periods in infancy (Stern, 1985; Fink, 1988; Kyrios, 2015), a ‘mature’ sense of self must be honed through life’s experiences. Indeed, the development of psychotherapeutic interventions attests to an understanding that enhancing self-awareness and adjusting to ever-changing realities is a long-term endeavour. As evidenced by research into behavioural and brain plasticity (Pascual-Leone et al., 2011; Keller & Just, 2016; Ponti, Peretto, & Bonfanti, 2008), the manner in which a person perceives surroundings is always susceptible to learning and development, with encounters in the world presenting limitless opportunities for fine-tuning attention and sensitivity to novel or previously undetected information (Gibson, 1979: 254). Below we argue that contexts that blur the distinctions between self and other, inner and outer, reality and non-reality, such as artistic or aesthetic pursuits involving intricate joint behaviour, may be especially helpful in this regard. We suggest that in terms of cognitive and affective outcomes they are analogous to the caregiver-infant interaction processes by providing a route to guide reality monitoring reflexes and self other attribution, leading to an adaptable sense of self. If correct, it follows that individual differences in self-other attribution and reality monitoring will be related to experience in these pursuits. Furthermore, long-term engagement in these pursuits may itself be predicted by the quality of early caregiver interactions.

1.8. Ambiguity-promoting behaviours: the case of music-making

In any social contexts, events tend to be co-produced, neither fully belonging to self or to other but resulting from the mutually regulated actions of both (Badino et al., 2014; Sebanz, Bekkering, & Knoblich, 2006; Konvalinka et al., 2010). Interaction always involves, indeed demands, a weakening of invariants. The coherence that typifies stimuli deriving from an individual agent and the incoherence that comes to be expected between autonomous agents is partially reduced as participants match to the varying intensities, timings, shapes or forms of each others' behaviour outcomes. In effect, this allows a quality of 'we-ness' to emerge. Those involved momentarily function as a larger 'whole' or system with its own emergent properties.

Music-making provides a particularly clear illustration of this. A musician, through thousands of hours of practice, learns to accurately coordinate highly intricate movements with those of others to produce specific auditory effects (Sloboda, 2000; Ericsson & Lehmann, 1996). The manner in which musical instruments are constructed and played indicates that controlling the degree of coherence and incoherence in sound (termed integration and segregation in this context) is of fundamental importance to all forms of music-making (Bregman, 1994:458, 674; Stein, 2005). In contrast to most listening experiences where the goal is to detect actual sound-sources in the environment, music often tries to create illusory sources or what Bregman (1994:460) calls "auditory chimeras": "It [music] may want the listener to accept the simultaneous roll of the drum, clash of the cymbal, and brief pulse of noise from the woodwinds as a single coherent event with its own striking emergent properties". This is achieved by going against invariants of coherence within and incoherence between entities or sound-sources. It is this skill that much of the effort of acquiring musical expertise is focused on – whether it be by learning to play in tune and in time with others or via the technical dexterity that enables an individual's sounds to segregate whilst blending with sounds produced by other musicians.

The literal meaning of symphony is 'sounding together' and there are many examples where the contributions of individual musicians are blurred by introducing coherence between separate entities. This is particularly evident in contexts such as

choirs or percussion ensembles where sound-sources are similar to one another. In the gamelan traditions of Southeast Asia, for instance, two or more musicians commonly perform interlocking patterns designed to be heard as deriving from a single coherent sound source (Tenzer, 1998; Bakan, 2007). This illusion of oneness is made possible by virtue of the coherence that exists between the sounds generated by the two musicians: their close proximity to one another, the similarity of the timbres produced by their respective instruments and in the coherence of intensity, timing, and pitch material between the contributions. Features specifying coherence, however, are at the same time balanced by cues that continue to point towards the incoherence that persists between autonomous agents both within and between sensory modalities. In other words it is still possible to see and partially hear that the two musicians are separate entities through (albeit slight) differences in spatial location, and in the variation of intensity, shape and form associated with each agent. The fact that this is an effortful task for many of us might attest to the social processing default of the human brain.

Conversely, by introducing incoherence characteristic of stimuli belonging to more than one entity, whether it be through abrupt changes of pitch range, intensity, timbre or spatial location, the sounds of a single musician (sound-source) can also split and be misperceived as deriving from separate entities. Partial segregation may be heard in many music traditions: examples include the abrupt changes of timbre produced by Chinese dizi flute music (Tsai, 2004), Mongolian diaphonic chatting (Lindestad et al., 2001), and the pseudo-polyphony in late Baroque music generated by rapidly switching between pitch range/register (Davis, 2006). Regarding the latter, Bregman (1994:464) writes: “these alternations were not fast enough to cause compulsory segregation, so the experience was ambiguous between one and two streams”. Frequently in music partial incoherence within entities is combined with partial coherence between them, with sounds belonging to one musician made to segregate from other sounds generated by the same musician whilst merging with components of sound belonging to other musicians.

Music, among other intricate joint behaviours such as dance, theatre and certain sports (McNeill, 1995; Pacherie, 2011; Sebanz, Bekkering, & Knoblich, 2006; Hove, 2008; Overy & Molnar-Szakacs, 2009), may therefore be seen as implicitly

promoting ambiguous perception, ensuring that entity boundaries are sufficiently blurred and that an equilibrium is reached between multimodal sensory conflicts that point towards togetherness, on the one hand, and separateness, on the other. As also described in relation to attunement processes during early development (often described using musical metaphors, e.g., proto-musicality, Malloch & Trevarthen, 2009), going against invariants in this way promotes a drive to test reality characterised by shifts between actual and illusory boundary alternatives.

When a person is directly *involved in* ambiguity-promoting behaviour, blurred boundaries extend not only to those between entities but also to feelings of agency. Take for example the experience of not being able to distinguish one's own voice from those belonging to other group members when singing in a choir. One moment it might feel that another's voice belongs to self (a case of over-attribution to self) and the next that one's own voice is not of our own making (over-attribution to other). This involves semi-coherence between internally- and externally-derived signals: the effects of others' behaviour partially match the manner in which one's own predictions, as well as the proprioceptive and affective sensations belonging to self, vary over time. Ambiguity and the associated feelings of a weakening of self-other boundaries, which has been referred to as boundary loss (McNeill, 1995), *we*-agency (Pacherie, 2011), coupling (Benzon, 2001), and rhythmic entrainment (Becker, 2004), may account for some of the powerful perceptual and emotional responses associated with certain joint behaviours (McLachlan 2000:67). Recounting memorable experiences, musicians as well as dancers commonly describe the feeling of oneness with others and the music, of losing themselves and the sense of their body to the moment, and even becoming possessed by an external force (Benzon, 2001:147). It is notable that, in many cultures, such behaviours are associated with, indeed used to induce, altered states of consciousness, such as trance, in which delusions of control and altered bodily sensations commonly occur (Rouget, 1985; Aldridge & Fachner, 2006; Becker, 1994).

It has been proposed that collective pursuits involving joint action may have evolved to establish and maintain group cohesion (Tarr, Launay, & Dunbar, 2014; Kirschner & Tomasello, 2010; Reddish, Fischer, & Bulbulia, 2013; Mithen, 2005). This has been supported by findings that associate movement synchrony between individuals

with increased feelings of social closeness and affiliation (Decety & Sommerville, 2003; Valdesolo & Desteno, 2011; Hove & Risen, 2009) – a process possibly mediated by the concomitant release of neurohormones such as endorphins (Dunbar et al., 2012; Launay, Tarr & Dunbar, in press). However, the experience resulting from participating in such joint activities is not typically one of complete and involuntary abandonment. This is because effortful cohesion demands self-awareness and some ability to integrate with others. Indeed, coordinating actions with others to an extent that permits the blurring of boundaries requires effective monitoring of self in relation to others to ensure that adjustments of behaviour that enable the desired emergent ambiguity to persist. For example, not being able to simultaneously monitor one's own voice and those of other ensemble members when singing in a choir – completely immersing in the illusion of oneness – is likely to result in going out of tune or out of time with others, reemphasising the differences that exist between participants. Thus, the performance of joint behaviours requires fluid shifts of attention between monitoring the outcomes of self, other, and the illusory composite sources of self with other.

1.9. Experience-driven plasticity of self

In keeping with findings from research into expert performance (Ericsson et al., 1993), the more time a person spends engaged in activities which challenge accurate self-other attributions, the better that person is likely to become at making such distinctions. If this is the case, individuals with extensive joint-action experience might be expected to be better than average at self-other processing. Music-making experience has already been associated with fundamental behavioural and cognitive changes related to agency that are reflected in functional as well as structural alterations in the brain (reviewed in Benz et al., 2015; Jäncke, 2009). For example, musical training has been associated with more pronounced auditory and motor system coupling (Zatorre et al., 2007), enhanced working memory (e.g., George & Coch, 2011), practice-induced efficiency in motor regions (Jäncke et al., 2000; Chen et al., 2012), and the refinement of cognitive control (e.g., Helmbold, Rammsayer, & Altenmüller, 2005; Lee, Lu, & Ko, 2007; Moreno & Besson, 2006). Longitudinal and experimental studies suggest that such improvements result from experience and

the intensity of training rather than from any innate musical predisposition (e.g., James et al., 2014; Hyde et al., 2009; Lahav, Saltzman, & Schlaug, 2007; Moreno et al., 2009). In fact, the reliability of such findings has meant that expert musicians have been identified as an ideal cohort to demonstrate mechanisms of experience-driven neuroplasticity (reviewed in Müente, Altenmüller, and Jäncke, 2002).

The idea that music-making develops self-monitoring abilities with observable impacts on brain development may have wider clinical implications. Many of the neural changes that result from extensive musical practice implicate functions and brain regions that have been highlighted in studies of individuals who report symptoms of schizophrenia. Importantly however, the neural patterns are in the opposite direction (Table 1).

For example, compared to individuals without musical experience, musicians show increased volume in the cerebellum (Hutchinson et al., 2003; Gaser & Schlaug, 2003; Amunts, 1997; Schlaug, 2001), premotor cortex (Gaser and Schlaug, 2003), hippocampus (Sluming et al., 2007), left planum temporale (Schlaug et al., 1995), Heschl's gyrus (Schneider et al., 2002), corpus callosum (Schlaug et al., 1995), and superior parietal areas (Gaser and Schlaug, 2003). Music-making expertise has also been associated with increased reliability and amplitude of mismatch negativity (MMN) (Rüsseler et al., 2001; Lappe et al., 2008), equilateral interhemispheric transfer (Patston et al., 2007), weaker cerebral blood flow (CBF) in the cerebellum during finger movements (Koeneke et al., 2004), lower CBF in the temporoparietal junction during improvised music-making (Berkowitz and Ansari, 2010), greater left hemisphere activity (Ohnishi et al., 2001), higher white matter integrity (Han et al., 2009; Halwani et al., 2011) and grey matter density (Han et al., 2009). In contrast, when compared to healthy individuals, people with schizophrenia tend to show reduced volume in the cerebellum (Bottner et al., 2005; Keller et al., 2003), premotor cortex (Douaud et al., 2007), hippocampus (Heckers & Konradi, 2010), left planum temporale (Petty et al., 1995), Heschl's gyrus (Hirayasu et al., 2000), corpus callosum (Woodruff et al., 1995), and superior parietal areas (Schiffer et al., 2010). Symptoms associated with this population have also been correlated to reduced MMN amplitude (Niznikiewicz et al., 2009), hemispheric imbalances (Gruzelier, 1984; Endrass et al., 2002), higher CBF in the cerebellum (Loeber et al., 1999), and

the temporoparietal junction during action attribution tasks (Farrer et al., 2004), reduced cerebral lateralization or right hemisphere dominance (Heckers, Goff & Weiss, 2002), and lower white matter integrity (Di, Chan & Gong, 2009) and grey matter density (Glahn et al., 2008).

To develop this idea further, the functional and anatomical differences between these cohorts would need to be tested directly. What is noteworthy and may justify such comparative investigation is that many of the results pointing in opposing directions implicate brain regions and processes that have been associated with agency (see, e.g., David et al., 2008). If the ability to accurately differentiate self from other at a perceptual level is malleable and can improve through practice, might such changes impact on the symptoms such as hallucinations and delusions that are specifically thought to be rooted in impairments in self-other processing (Frith, 2000; Jeannerod, 2009; Bentall et al., 2007)? To date there is evidence to suggest music's effectiveness in suppressing symptoms of psychosis (Silverman, 2003; Peng, Koo & Kuo, 2010; Na & Yang, 2009; Gold et al., 2009), with musical competence negatively related to symptom severity in schizophrenia (Kantrowitz et al., 2013). There are also precedents for using music as a tool for neuro-rehabilitation (reviewed in François et al., 2015; Whipple, 2004; Raglio et al., 2008).

Table 1.1. Comparing differences in brain structure and function between musicians compared to non-musicians and schizophrenia patients compared to controls

Musicians compared to non-musicians	Schizophrenic patients compared to controls
Increased corpus callosum size (Schlaug et al., 1995)	Reduced corpus callosum size (Woodruff et al., 1995) Reduced interhemispheric transmission (Endrass et al., 2002)
Equilateral interhemispheric transfer for visual information (Patston et al., 2007)	Hemispheric imbalances in schizophrenia. (Gruzelier, 1984)
Leftward planum temporale asymmetry (Schlaug et al., 1995)	Reversal of normal asymmetry (left larger than right) of the planum temporale surface area (Petty et al., 1995).
Larger tract volume and higher fractional anisotropy values of the right and left arcuate fasciculus (Halwani et al., 2011)	Reduced fractional anisotropy in the left uncinate fasciculus and left arcuate fasciculus (Burns et al., 2003); White matter reduction (Di, Chan & Gong, 2009)
Higher gray matter density and white matter integrity (Han et al., 2009)	Reduced gray matter density in bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus. (Glahn et al., 2008)

Greater cerebellar volume (Hutchinson et al., 2003; Gaser & Schlaug, 2003; Amunts, 1997; Schlaug, 2001)	Reduced cerebellar volume (Bottner et al., 2005; Keller et al., 2003)
Weaker hemodynamic responses in the cerebellum (Koenke et al., 2004)	Higher cerebellar blood volume (Loeber et al., 1999)
Increased hippocampal volumes (Sluming et al., 2007)	Smaller hippocampal volumes and abnormal hippocampal activity (Heckers & Konradi, 2010)
Right temporoparietal junction deactivation during melodic improvisation (Berkowitz and Ansari, 2010)	Higher baseline activation level in the inferior parietal lobule (Farrer et al., 2004; Spence et al., 1997); Reduced functional connectivity of the temporoparietal area. (Vercammen et al., 2010)
Amusia due to Right Temporoparietal Infarct. (McFarland & Fortin, 1982)	Anatomical abnormalities of the Temporoparietal junction linked to auditory hallucination (Plaze et al., 2009)
Increased MMN amplitude and reliability (Rüsseler et al., 2001; Lappe et al., 2008)	Reduced MMN amplitude (Niznikiewicz et al., 2009)
Increased heschl gyrus gray matter volume (Schneider et al., 2002)	Reduced heschl gyrus gray matter volume (Hirayasu et al., 2000)
Increased gray matter volume in premotor cortex (Gaser and Schlaug, 2003)	Reduced gray matter volume in premotor cortex (Douaud et al., 2007)
Left hemisphere dominance (Ohnishi et al., 2001)	Right hemisphere dominance (Heckers, Goff & Weiss, 2002)
Volume increases in superior parietal areas (Gaser and Schlaug, 2003)	Volume decreases in superior parietal regions (Schiffer et al., 2010)

1.10. Wider discussion

It is suggested here that a resilient sense of self, essential to mental health, equates to a flexible self and, as such, requires development in contained environments which afford ongoing opportunities for reality-testing. Experience in contexts that sustain a high level of ambiguity and allow individuals to ‘play’ with actual and illusory object boundaries, particularly those that exist between control belonging to self and other, provide optimal conditions for forging a sense of self and provide a buffer to the inevitable individual/internal and environmental changes and stressors that occur throughout life.

Somewhat paradoxically, it may be by weakening self-other and internal-external boundaries – physical and agentic limits and mental attributions – that an individual comes to an enhanced awareness of, and ability to negotiate, perceived shifts in such boundaries. Epstein (1999) suggests that academic psychology has traditionally

focused on the individual self as something to be strengthened, without sufficient consideration given to the everyday reality of more fluid, unintegrated states of mind, which have typically only been associated with early infancy (the imaginary friend) and mental illness. As with the young child at play, adult self-awareness routinely vacillates to include states of bodily dissociation, as, for example, when one escapes into the imaginary world of a novel or film (Rochat, 2003). Comparing the Western notion of the self in relation to understandings in Buddhist philosophies, Epstein (1999: 85) contrasts the self as something to be “developed or improved throughout its one-way journey toward separateness” in the former, to the self as variously “expanding and contracting, coalescing and dissolving, separating and merging” in the latter. Milner (2010: 181) concurs that experiences of loss of self, for example as achieved through play, meditation, or absorbed participation in music and arts, should not be dismissed as a regression to an earlier, less developed state, but as a normal phenomenon that enriches perception through the re-encountering of self in novel ways: “there is a plunge into no-differentiation which results (if all goes well) in a re-emerging into a new division of me-not-me, one in which there is more of the ‘me’ in the ‘not-me’, and more of the ‘not-me’ in the ‘me’”. In this way, playing with realities and non-realities and in the gap between self and non-self, without confusing them lies at the heart of creativity as a dimension of ordinary wellbeing. In contrast to involuntary experiences such as the distressing hallucinations and delusions associated with mental illness, purposive ambiguity-promoting behaviours, involve a deliberative and ultimately contained surrendering of conscious control. The extent to which a participant is able to monitor and influence when and how self disintegrates and/or merges with others may make the difference between an ambiguous context that is playful, creative, and promotes engagement from one that is anxiety-inducing, and potentially annihilating.

Not all pursuits are equal in this regard. With reference to collective activities Pacherie (2011) provides a helpful distinction between ‘hierarchical’ and ‘egalitarian’ joint action. Using the Western symphony orchestra as an illustration, she argues that in the former, tasks are centralised and specialised, with individual musicians limited in their capacity to control overall outcomes and instead reliant on diktats from the conductor and the constraints imposed by the score/composer. In more egalitarian music systems (often reflecting the collectivist societal structures in

the cultures in which these systems tend to emerge), such as African drumming, jazz and gamelan, governance tends to be distributed across the ensemble. Participants are called upon to predict and monitor individual and combined outcomes, controlling for themselves to differing degrees the variation in coherence and incoherence in relation to one another. This is more reminiscent of the reciprocal dynamic that exists between caregiver-infant interactions where the infant is an active agent and it is safe to momentarily ‘go to pieces’ or merge with the other, “without falling apart” (Epstein, 1999). Thus, distinct forms of music-making or joint action afford qualitatively different subjective experiences of self and other and are likely to mould self-development in diverse ways. In more general terms, although all human interactions involve the need to make behavioural decisions with inadequate information, cultures or communities of practice can promote ambiguity to greater and lesser extents. This may be reflected in the tools and symbols that are used to relate to others. For example, anthropologist Edward Hall (1992) describes languages as being lower or higher context. The former refers to linguistic information that is complete, explicitly contained within the message itself, while a higher context language is one that relies on a greater degree of implicit shared knowledge and interpretation from recipients (Hall 1992:229-230). Understanding and questioning the quality of attunement promoted by social, cultural and political structures, the extent to which practices promote or thwart ambiguity between self and other may inform conceptualisations of mental health and strategies put in place for addressing mental illness.

1.11. Conclusions and future directions

This paper argues that ambiguity (as fundamental characteristic of many everyday social encounters) plays a key role in developing the sense of self and in learning to differentiate between the boundaries of objects including those that exist between self and other as agents in the world. We propose that engagement in challenging activities that require self-other differentiation may provide optimal conditions for refining reality-testing abilities related to self-other processing. With cross-modal attunement in early infancy framed as one such ‘healthy’ ambiguous context that blurs the boundary between caregiver and infant, the argument positions

vulnerability to psychosis-related phenomena within this developmental framework (Bentall et al., 2007). However, the case is also made that attribution competencies negatively associated with hallucinations and delusions in previous research may be malleable and improve through practice. Indeed, certain collective behaviours that put the sense of self into question by introducing a high degree of coherence between autonomous agents (e.g., such as music-making, dance and certain sports), may be understood as having the functional role of promoting social bonding by improving self-other monitoring capabilities. Experience in ambiguity-promoting contexts may also allow those involved to become better able to tolerate and creatively ‘play with’ modulating self-other sensations, freeing up capacity to refine appropriate reality-testing reflexes. This may serve to reduce the likelihood of experiencing unsolicited and distressing misattributions associated with psychosis.

The argument presented here allow specific hypotheses to be generated and tested using behavioural and neuroimaging methods. For example, one over-riding question is whether experience in situations of intricate joint action (such as music-making) positively correlates with the ability to distinguish between action outcomes belonging to self and other, particularly in ambiguous contexts, in contrast to hallucination proneness. What are the neural correlates of this type of ambiguity and of competencies related to self-other differentiation? One might then ask whether improvements in self-other processing, at a perceptual level, generalises across domains in adulthood. If so, would such improvement impact on phenomena such as hallucinations that have been associated with reduced attribution performance? Related to this are questions around the optimal conditions for bringing about change in self-other processing skills – for example, what types of activities, and constituent elements therein, work best? Such research may not only offer insights into mechanisms mediating the emergence of mental health difficulties, but also has the potential to extend the range of therapeutic possibilities. As Postmes et al. (2014) argue, models of self-disorders such as schizophrenia that focus on lower-level perceptual mechanisms are under-represented in research and clinical literatures. Despite evidence for inter-dependency between top-down and bottom-up processes (e.g., Adcock et al., 2009; Shea, 2014), few therapies target ‘lower’ configurations of self (e.g., core sense of self) that involve more primitive sensations of the body as a

coherent entity/agent and its relation to surroundings including other agents over time. We believe that more insight into behavioural and neural responses to ambiguity will contribute to the design of environments and opportunities that maximise such development and will increase our understanding of self-disorders more generally.

1.12. References

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CHAPTER 2

Ambiguity between self and other: Individual differences in action attribution

[de Bézenac, C. E., Sluming, V., O’Sullivan, N., & Corcoran, R. (2015). Ambiguity between self and other: Individual differences in action attribution. *Consciousness and Cognition*, 35, 1-15.]

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2.1. Abstract

Individuals differ in their ability to attribute actions to self or other. This variance is thought to explain, in part, the experience of voice-hearing. Misattribution can also be context-driven. For example, causal ambiguity can arise when the actions of two or more individuals are coordinated and produce similar effects (e.g., music-making). Experience in such challenging contexts may refine skills of action attribution. Forty participants completed a novel finger-tapping task which parametrically manipulated the proportion of control that ‘self’ versus ‘other’ possessed over resulting auditory tones. Results showed that action misattribution peaked in the middle of the self-to-other continuum and was biased towards other. This pattern was related to both high hallucination-proneness and to low musical-experience. Findings suggest not only that causal ambiguity plays a key role in agency but also that action attribution abilities may improve with practice, potentially providing an avenue for remediation of the positive symptoms of schizophrenia.

Keywords: Action attribution; agency; ambiguity; action-outcome discordance; hallucination proneness; joint-action; music-making; misattribution; schizotypy

Highlights

- Method for examining action attribution in ambiguous conditions
- Self-to-other continuum: manipulating the proportion of tones generated by self versus other
- Misattribution peaked in ambiguous conditions biased towards other
- Hallucination proneness increased misattribution in ambiguous conditions
- Musical experience reduced misattribution in ambiguous conditions

2.2. Introduction

The ability to distinguish between events caused by the actions of self from those caused by others is a fundamental aspect of social behaviour, contributing to self-consciousness and sense of agency (Gallagher, 2000; Moore & Fletcher, 2012; Haggard, 2005; Tsakiris et al., 2007; David et al., 2008; Synofzik et al., 2008). The ‘comparator model’ suggests that we monitor ‘who is in control of what’ by comparing predicted to actual action outcomes. If a sensory outcome matches the predicted result of an action of self the event is experienced as self-initiated. In the case of a discordance, the act is attributed externally (Wolpert & Miall, 1996; Frith et al., 2000; Von Holst, 1954; Trinity & Sommer, 2008). Although likely to involve higher-order retrospective judgements (such as the allocation of credit or blame) and intention formation (Pacherie, 2006; Wegner, 2003; Gallagher, 2010), this comparator mechanism is thought to be fast, automatic and perceptually-driven (Frith, 2005).

However, individuals’ traits, mental states, intentions, beliefs, and expectations can result in errors of attribution (misattributions) (Wegner, 2003; Farrer et al., 2008;

Dijksterhuis et al., 2008; Synofzik et al., 2006; Sato, 2009). In particular, the inability to know what is self-produced from what is externally caused constitutes one of the core deficits of schizophrenia, most clearly reflected in passivity phenomena including delusions of control and auditory verbal hallucinations (Spence et al., 1997; Parnas & Handest, 2003; Jeannerod, 2009; Ditman & Kuperberg, 2005; Lindner et al., 2005; Frith, 2005; Woodruff, 2004). Evidence for perturbed attribution in this group comes from a number of different paradigms, including feedback distortion typically using delay or spatial displacement to introduce a discordance between a participant's action and the visual, tactile or auditory outcome of those actions (Farrer & Franck, 2007; Blakemore et al., 2000; Franck et al., 2001; Sato & Yasuda, 2005). Compared to healthy controls (HC), schizophrenic patients (SZ) make more errors of attribution, with a tendency to misattribute their actions to another agent (although some studies have show a bias towards self (e.g., Daprati et al., 1997; Franck et al., 2001)). These findings are consistent with those from studies using other source-monitoring paradigms (Bentall et al., 1991; Baker & Morrison, 1998; Brebion et al., 2000; Johns et al., 2001, Farrer & Franck, 2007). As increased misattribution has also been observed in healthy individuals with schizotypal personality traits (Asai et al., 2008; Johns et al., 2010; Sugimori et al., 2011; Strauss, 1969), dimensional measures of psychosis-proneness can be used to explore the attributional biases associated with psychosis without the confounding effects of medication or long-term chronic illness (Raine, 2006).

While the focus of much of the clinically-oriented agency literature has been on mechanisms internal to the perceiver (see review by Moore & Fletcher, 2012), misattribution can also be driven by external, situational factors (Wegner, 2002, 2003). For example, when one coordinates behaviours/thoughts with others to achieve a common goal, actions often take place at approximately the same time, in close proximity with complementary effects (Farrer & Frith, 2002; Sebanz et al., 2006). This can lead to causal ambiguity, where distinguishing between self-control and other-control is not clear-cut. According to the comparator model, such situations can introduce discordance between action and outcome which are neither negligible (where self-control would be inferred) nor substantial (where other-control would be inferred), but somewhere in between. This middle ground, or state of semi-discordance, effectively limits the amount of information available for self-other

differentiation, making moments of misattribution more likely where either an individual experiences control over outcomes that belong to others or experiences loss of control over the results of one's own actions. The ouija board where the commingled actions of two or more individuals blur the locus of control is an example of this latter attribution to other bias (see Ansfield and Wegner, 1996). Studies that examine behaviours involving intricate between-individual coordination (such as music-making, dance, marching, rowing) have highlighted the potential for such behaviour to weaken the boundary between self and other (Benzon, 2001; McNeill, 1995; Pacherie, 2011; Hove, 2008). Furthermore, there is growing, converging evidence suggesting that the sense of self is a surprisingly flexible, ongoing construct, open to rapid influence from encounters with surroundings (see Clark, 2003). However, little is known about the role that ambiguity plays in action attribution, particularly in relation to individual-differences such as schizotypy (Gallagher, in press; Fukushima et al., 2013). Given that individual differences are likely to be most pronounced in ambiguous contexts where attribution is most challenging, understanding causal ambiguity has potential to shed light on agency-related traits or deficits.

Previous studies have tended to take a categorical approach to agency, either by not including conditions between self and other or by asking participants to provide binary (yes/no) rather than graded attribution responses. Findings from feedback distortion studies that do include intermediate conditions between self and other (e.g., Sato & Yasuda, 2005; Franck et al., 2001; Farrer et al., 2003; 2004) support the view that processes underlying action attribution are continuous being based on sensorimotor signals that vary continuously (e.g., spatial and temporal features of stimuli). In a PET imaging study, Farrer et al., (2003) asked subjects to draw random lines using a joystick under four conditions that provided varying degrees of control over the results of actions. These authors found that the degree of a subject's control over action outcomes modulates activity *continuously* in the insula (negative correlation with loss of control) and the right inferior parietal lobe (positive correlation with loss of control). However, this pattern was not seen in participants with positive symptom schizophrenia who showed significantly less functional sensitivity to the manipulation (Farrer et al., 2004). This supports the idea that the feeling of being the cause of an event may be better represented along a self-to-other

continuum. A closer look at Farrer et al.'s findings reveals that the most significant differences between healthy and schizophrenia participants occurred in the two conditions between self and other suggesting that passivity phenomena might be best understood as an impairment arising in the context of low value information.

More generally, coping with ambiguity plays an important role in a range of emotion and psychopathological disorders including general anxiety disorder (Buhr & Dugas, 2002), obsessive-compulsive disorder (Tolin et al., 2003), and schizophrenia (Broome et al., 2007; Freeman et al., 2008). Imaging research has implicated a network of brain regions involved in conflict detection and resolution in tasks that manipulate ambiguity (Krain et al., 2006), including dorsolateral prefrontal cortex (DLPFC; Huettel et al., 2005), inferior parietal lobe (IPL; Britz et al., 2009; Volz et al., 2003), amygdala (Hsu et al., 2005; Zaretsky et al., 2010), and anterior cingulate cortex (ACC; Botvinick et al., 2001; Stern et al., 2010; Critchley et al., 2001). These same areas have also been implicated in both sense of agency and the pathogenesis of schizophrenia (Minzenberg et al., 2009; Yildiz et al., 2011; Cannon et al., 2002; Potkin et al., 2009; Callicott et al., 2000; Zhou et al., 2007; Adams & David, 2007; Eisenberg & Berman 2010) and social cognition (Weissman et al., 2008; Adolphs, 2001). – a domain also consistently shown to be deficient in schizophrenia (e.g., Green & Horan, 2010).

While the study of neurological disorders and mental illness has contributed significantly to empirical and theoretical advances in agency research, the investigation of individuals who are better than average at distinguishing between actions of self and other is under-explored. A possibility in keeping with findings from research into expert performance (Ericsson et al., 1993) is that the more time a person spends engaged in activities which require accurate self-other distinctions to be made under sufficiently challenging conditions, the better that person is likely to become at making such distinctions. As previously noted, joint-action makes self-other differentiation challenging, creating ambiguity about the action source. At the same time, the ability to distinguish self from other contributions or outputs is typically a prerequisite for effective between-individual action coordination. Given this imperative, action attribution abilities may develop alongside, or even as a result of, engaging in ambiguity-promoting activities such as those requiring intricate

between-individual coordination. If this is so, expert joint-actors, such as musicians, and dancers, may have more honed attribution skills than individuals with less experience of joint-action.

A musician, through thousands of hours of deliberate practice, learns to accurately coordinate highly intricate movements with others to produce specific auditory effects (Sloboda, 2000; Ericsson & Lehmann, 1996). Consistent with the literal meaning of *symphony* – ‘sounding together’ – music from around the world is often deliberately structured to blur the contribution of individual musicians in the resulting sonic texture. What is often desired is to hear composite lines, that themselves don’t exist in reality, made up of the combined actions of multiple individuals (Bregman, 1990). Conventions of counterpoint, harmony, of melodic and temporal structure, may be understood as ways of promoting causal ambiguity by ensuring a high level of ‘togetherness’ between musicians (de Bezenac, 2000). In fact, much of the effort of acquiring musical expertise is focused around achieving this goal, whether by learning to play ‘in tune’ and ‘in time’ with others or by acquiring the technical dexterity necessary to commingle one’s action with others in a sufficiently intricate manner. This means that misattribution during music-making is more likely than during involvement in other more solitary activities. At the same time, the ability to play music does require that musicians know what parts of the sound are being produced by self versus other. How else could they monitor or correct their actions in relation to those of others? Behavioural and imaging studies show a pronounced auditory and motor system coupling in musicians (Zatorre et al., 2007). We argue that the combination of requiring action-attribution in contexts that make it difficult to attribute means that music-making is an activity that provides ideal conditions for sharpening self-other differentiation abilities.

If musical experience is found to negatively correlate with misattribution, it would suggest that self-other action attribution abilities are mutable throughout life. Given that passivity phenomena are thought to be rooted in misattribution (Frith 2000; Jeannerod, 2009), it presents the possibility that engaging in intricate joint-behaviour could have protective or remediative effects, explaining findings from music therapy research of music’s effectiveness in suppressing symptoms of psychosis (Silverman, 2003; Peng et al., 2010; Na & Yang, 2009), as well as findings showing musical

competence to be negatively related to symptom severity in schizophrenia (Kantrowitz et al., 2013).

In the neuroscience literature, a number of differences have been found in musicians compared to non-musicians, such as: increased volume in the cerebellum, premotor cortex, superior parietal areas and Heschl's gyrus (Gaser & Schlaug, 2003a; 2003b), higher white matter integrity (Halwani et al., 2011) and gray matter density (Han et al., 2008), as well as lower cerebral blood flow in the temporoparietal junction (Berkowitz & Ansari, 2010) and increased reliability/amplitude of mismatch negativity (Rüsseler et al., 2001; Lappe et al., 2008). Interestingly, these structural and functional differences have all also been associated with schizophrenia but pointing in the opposite direction (Bottmer et al., 2005; Douaud et al., 2007; Di et al., 2009; Hirayasu et al., 2000; Glahn et al., 2008; Farrer et al., 2004; Niznikiewicz et al., 2009). Taken together, these findings point towards a possible link between music-making and mechanisms underlying schizophrenia.

To achieve a clearer understanding of the relationship between internal and external cues across an entire self-to-other continuum and so deepen our knowledge of agency in health and psychosis (Moore & Fletcher, 2012), an objective and continuous measure of sense of control (self to other) that participant's subjective attribution ratings can be measured against must be developed. In traditionally used feedback distortion paradigms, it is not obvious how much distortion (delay or spatial displacement) is required for stimuli to objectively belong to other or to be considered ambiguous. Farrer et al. (2003; 2004), for example, spatially distorted results of the participant's movements in steps of 25 degrees for conditions 2 and 3, and used the results of another individual's actions for the 4th condition, making it impossible to assert that differences between successive conditions were equal. Furthermore, previous studies have tended to keep the amount of distortion constant within trials (e.g., 25 degrees of spatial displacement), often by restricting trials to single events. Apart from the risk of confounds associated with adaptation effects (Honda et al., 2012; Cunningham et al., 2001), consistent distortion can exclude a ubiquitous source of ambiguity in attribution. In most dynamic contexts outside experimental settings, for instance during joint-action, information for both self and other is simultaneously available for perception. This means that successive stimuli

can point to varying extents in opposing directions, for example, with one stimulus pointing towards self while the next points towards other. Overall sense of agency is likely, in part, to be determined by weighing up stimuli over time, rather than processing discrete events separately, making it easy to conceive of agency as a matter of degree. Ambiguity may be said to increase as the proportion of action belonging to self and other becomes more equal, resulting in semi action-outcome discordance. The manner in which agency builds up over time has not been a focus in previous research and could help fill the conceptual gap between agency as it functions at a sensorimotor, perceptual level and at a higher-level, such as the overall control that a person feels over their lives (Gallagher, in press).

The purpose of the present study was to examine the relationship between subjective and objective control, with a particular focus on causal ambiguity – the middle of the self-to-other continuum. Using probability, we parametrically manipulated the proportion of control that actions of self versus other had over an auditory tone associated with finger taps during a series of ten-second trials. Attribution error (misattribution) was defined as the difference between the proportion of control that participants felt they had (attribution rating) compared to the control that they actually had. As attribution is likely to be most challenging in ambiguous contexts, misattribution was expected to peak in the middle of the discordance continuum (semi-discordance: 50% self; 50% other). We examined misattribution in relation to individual differences thought to be associated with lower attribution abilities, hallucination proneness (LSHS-R), as well as higher abilities, musical experience. We expected misattribution to be particularly related to hallucination proneness in the middle of the self-to-other continuum, based on the hypothesis that perturbed attribution previously identified in patients with positive symptoms and schizotypal tendencies may be understood as an inability to deal with causal ambiguity. In contrast, individuals who spend a great deal of time in contexts that make self-other differentiation necessary but often challenging (e.g., intricate joint action) are likely to become better at differentiating acts of self from those of others. We, therefore, predicted that years of musical experience would be negatively associated with misattribution, again, particularly in ambiguous contexts.

2.3. Methods

2.3.1. Participants

The sample comprised 40 participants (11 females; 30 right-handed) with a mean age of 29 years ($SD = 6.3$; range, 20-42). They were recruited from staff and students at the University of Liverpool and, to insure sufficient variability in musical experience, a pool of Manchester-based musicians matched for age and education. All reported normal, or corrected-to-normal, vision and hearing, somatosensory perception and reported no history of mental illness or neurological abnormalities. The study was approved by the ethics committee of the University of Liverpool and conducted in accordance with committee policies.

2.3.2. Stimuli and apparatus

Stimulus presentation and participant response collection were managed using Pure Data (a real-time graphical programming environment: <http://puredata.info/>) and a MacMini computer. The auditory stimuli were presented at 65 dB diotically through headphones (PX-660, Pro-Luxe) and consisted of an auditory tone (a cosine wave, 262 HZ; 100 ms duration; 20 ms onset ramp; 5 ms offset ramp). This tone could either be generated by participant finger taps [self] (inherent delay of 15ms) or by the participants' 50 previous inter-tap intervals played back in a random order [other]. There were 10 different conditions corresponding to the proportion of control that self versus other had over tones within trials. This proportion was manipulated in the following way: a random number between 0 and 90 was generated on every tap; each condition was associated with a threshold above which tones generated by self would be heard and below which tones generated by other would instead be heard. For example, with a threshold of 90 all tones belonged to self (condition 1: maximal action-outcome concordance) (Fig. 2.2 C1), while tone control belonged exclusively to other when the threshold was set to 0 (maximal discordance) (Fig. 2.2 C10). A threshold of 50 resulted control randomly shifting (following a tap) between self and other (condition 5: semi-discordance) (Fig. 2.2 C5) (see Table 2.1 for the threshold used in each condition). This method allowed the proportion of tones belonging to self and other to be manipulated systematically in 10 equal steps (conditions). Fig. 2.2 shows temporal relationships between self-produced taps (Self), tone onsets (Tone) and other-produced taps (Other) for one arbitrarily chosen participant in

conditions 1 (C1), 5 (C5) and 10 (C10). Note the synchrony between self and tone in C1, other and tone in C10, and the semi-synchrony between self and tone and between other and tone in C5 (see Table 2.1).

2.3.3. Procedure

The same quiet, dimly lit room was used for all experimental sessions. Participants were asked to use the index finger of their dominant hand to perform a series of irregular, Morse code-like taps whilst listening to a sequence of tones. A recorded example was provided to ensure that density of taps was similar across participants. Participants were explicitly told that tones could either result from their own actions/taps, the recorded actions/taps of another individual, or varying mixtures of both. After each trial, consisting of 10 seconds of tapping, participants were asked to assess the proportion of control that they felt belonged to self versus to other along a continuum, using its entire range. This consisted of an empty rectangle (12x3cm) with the word “self” displayed on the left and “other” on the right. Following a mouse click, a vertical line would appear at the position of the click and participants could adjust their response before clicking on the “Submit” button that would trigger a three second countdown to the following trial. After a 3-minute practice session to ensure that the task was fully understood, each participant completed a total of 50 trials made up of 5 repetitions of each of the 10 conditions. These were presented to participants in a pseudo-random order, with the constraint that consecutive trials were at least two conditions apart (e.g., C2 could not be followed by C1 or C3) and that each set of 10 conditions were completed before proceeding to the next set.

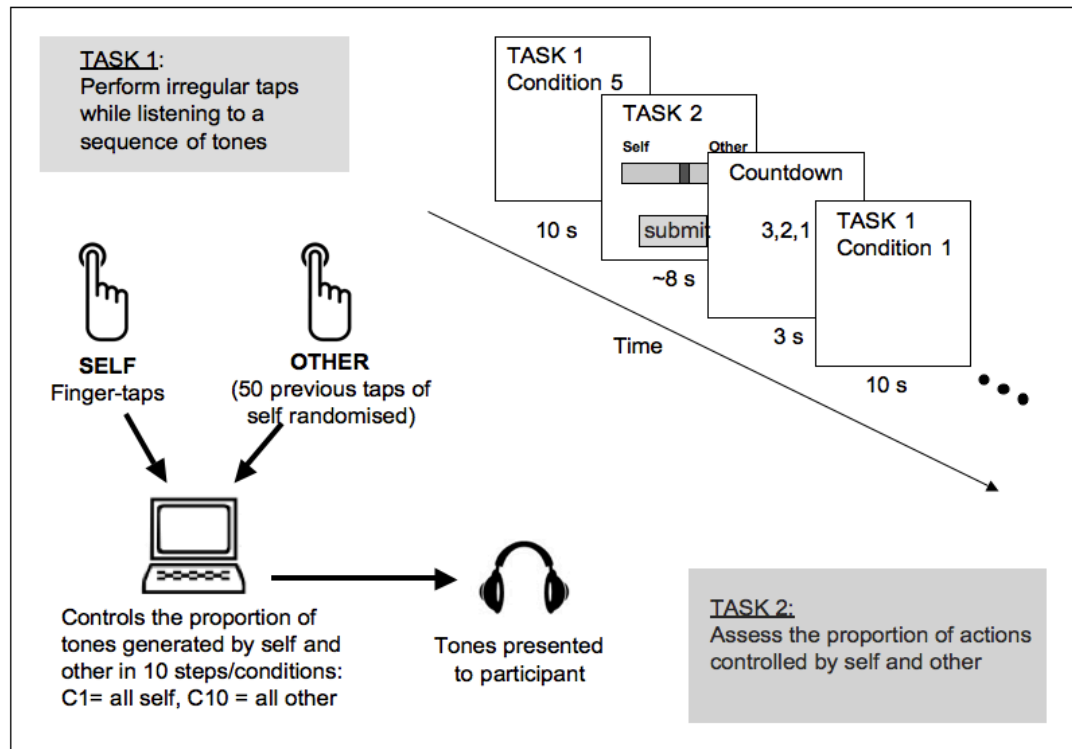


Fig. 2.1. Illustration of the experimental task.

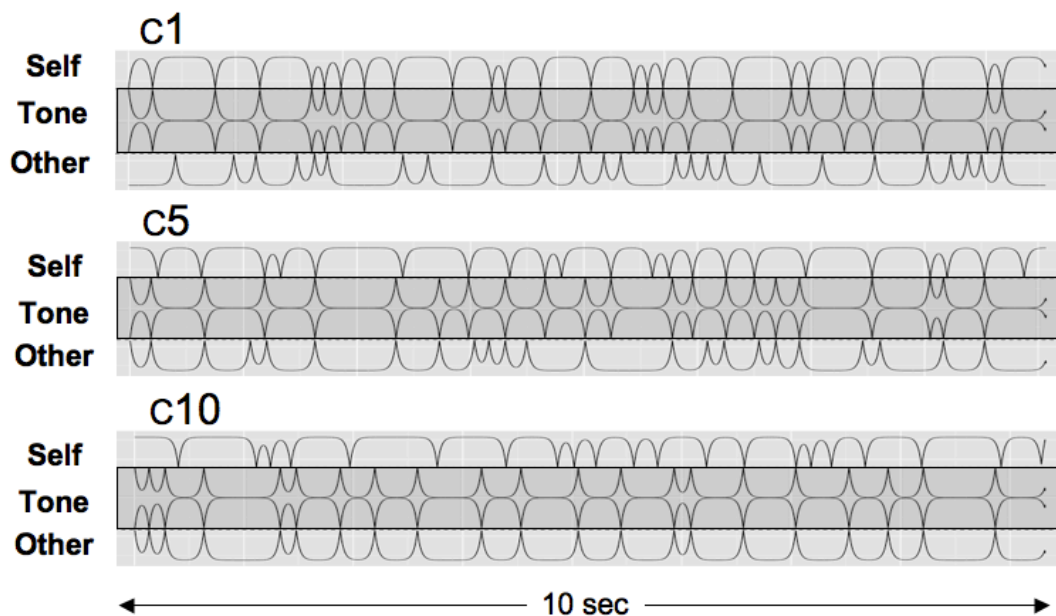


Fig. 2.2. Temporal relationships between self-produced taps (Self), tone onsets (Tone) and other-produced taps (Other). Data shown are from one arbitrarily chosen participant in condition 1 (C1), 5 (C5), and 10 (C10). Onsets have been smoothed to produce a wave-like shape and positioned to make temporal relationship apparent (i.e., 'Self' inverted and 'Tone' mirrored).

2.3.4. Individual difference data

After the experimental task, participants completed the Launay-Slade Hallucination Scale (Revised) (LSHS-R) (Launay & Slade, 1981) – a frequently used reliable measure of predisposition to hallucinations in normal individuals (Aleman et al., 1999; Bentall & Slade, 1985; Levitan et al., 1996). The scale comprises 12 items each scored on a five-point Likert scale. Items describe clinical hallucinatory experiences (e.g. ‘In the past, I have had the experience of hearing a person’s voice and then found that no one was there’) or *sub-clinical*, intrusive mental events (e.g. ‘The sounds I hear in my daydreams are usually clear and distinct’). The scale has a range of 0 to 48 with higher scores indicating greater predisposition to hallucination-like experiences.

Participants were then interviewed by a music pedagogue to assess the extent of their music-making experience. The semi-structured interview lasted approximately 5 minutes. The interviewer began by asking the participant: “How many years of music-making do you have?” This was followed by more in-depth questions relating to (1) formal training (2) informal experience and (3) the role that music has generally played in their lives. Responses were used to check for over- and under-estimations in self-reported years of musical experience.

2.4. Results

2.4.1. Paradigm validation

With data pooled over all participants, the mean number of actions per trial was 30 (SD = 7.), the mean number of tones per trial was 32 (SD = 9), and mean attribution rating (scaled from 0-1) was .52 (SD = .33). To assess how the above measures varied across conditions, correlation tests were conducted for each participant separately. There was a small tendency for participants to perform less taps as conditions increased (reduced control over tones), mean $r = -0.28$ (SD = 0.18). The number of tones per trial did not vary with condition, mean $r = -0.11$ (SD = 0.10), suggesting that apart from action-outcome discordance stimuli were similar across conditions.

To validate the probability-based manipulation, a measure of synchrony between the onsets of the participant taps and auditory tones was calculated. Onset time-series for both measures were first smoothed (butterworth low-pass filter: order = 1, band = 0.01) (see Fig. 2.2 to see the resulting wave), then correlated with one another for each trial and for each participant. Mean correlation between synchrony and condition was $r = -0.95$ (SD = 0.033), indicating that the manipulation was successful and that conditions 1 to 10 provided a reliable and systematic measure of action-outcome discordance.

With data pooled over all participants, mean attribution (scaled from 0, indicating 100% self, to 1, indicating 100% other) increased with condition (discordance) while the standard deviation of attribution peaked near middle conditions 3, 4, and 5 and was lowest in condition 1 (Table 2.1). All participants were included in the analysis on the basis of their significant positive correlation values between attribution rating and condition, mean $r = 0.76$ (SD = 0.11). Using a t-test, these correlation values were found to be significantly greater ($t = -4.63$, $df = 77.6$, $p < 0.001$) than those obtained when using a mean split binary measure of discordance (mean $r = 0.64$). This suggests that individuals are able to better discriminate between self and other in a continuous as opposed to categorical manner.

Misattribution was used as a measure of performance on the task and calculated as the difference between attribution rating and condition (rescaled from 0 to 1). Positive values (shown to peak in condition 4 in Table 2.1) indicate a bias towards other while negative values a bias towards self (seen from condition 7 onwards). Table 2.1 also shows that the standard deviation of misattribution peaked in conditions 4 and 5.

Table 2.1. Summary statistics by condition (C1 to C10) with data pooled over all participants

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Manipulation threshold	90	80	70	60	50	40	30	20	10	0
Correlation between tap (self) and tone	1	0.87	0.75	0.65	0.57	0.46	0.38	0.26	0.13	0.01
SD of tap-tone correlation	(0)	(0.07)	(0.12)	(0.11)	(0.08)	(0.09)	(0.11)	(0.12)	(0.09)	(0.1)
Mean attribution	0.02	0.17	0.35	0.48	0.54	0.64	0.66	0.73	0.80	0.84
SD of attribution	(0.09)	(0.17)	(0.25)	(0.25)	(0.25)	(0.24)	(0.24)	(0.22)	(0.21)	(0.2)
Mean misattribution	0.2	0.05	0.13	0.14	0.09	0.08	0	-0.04	-0.09	-0.16
SD of misattribution	(0.8)	(0.17)	(0.24)	(0.25)	(0.25)	(0.23)	(0.24)	(0.21)	(0.2)	(0.2)

Descriptive statistics for hallucination proneness (HP) and years of musical experience (ME) are shown in Table 2.2. Self-reported years of musical experience was used as the final ME score in every case, as responses prompted by the semi-structured interviews confirmed that all participants had made sufficiently reliable estimations. HP and ME did not significantly correlate with one another $r = -0.16$ ($t = -1.0105$, $df = 38$, $p\text{-value} = 0.3186$), meaning that observed differences between the two measure in relation to the task was not simply a reflection of significant correlation between them.

Table 2.2. Descriptive statistics of questionnaire and interview data

	Mean	SD	Min	Max
Hallucination proneness (LSHS-R)	23.2	5.4	14	34
Musical Experience (in years)	12.4	8.2	3	26

2.4.2. Overall misattribution

Fig. 2.3 shows the misattribution profile for all 40 participants with data pooled over the 10 conditions. Between-individual variation may be seen in at least two distinct ways: (1) how centered scores are around 0 (dotted line indicating no error), reflected in the standard deviation of misattribution (e.g., compare participants 1 and 15); and (2) the direction of bias towards self (right heavy distribution) or other (left heavy distribution), reflected in mean misattribution (e.g., compare participants 4 and 23).

A multiple regression revealed that the overall variability in attribution responses, as measured by the standard deviation of misattribution, increased with HP, $b = 0.002$, $t = 2.17$, $p = 0.03$, and decreased with ME, $b = -0.002$, $t = -2.06$, $p = 0.046$ ($R^2 = 0.22$, $F(2,37) = 1.2$, $p = 0.009$). Examining bias towards self and other, a positive trend was observed between HP and mean misattribution, indicating a general bias towards other, but this failed to reach significance, $b = 0.003$, $t = 1.527$, $p = 0.13$, as did the negative relationship between mean misattribution and ME, $b = -0.002$, $t = -1$, $p = 0.32$ ($R^2 = 0.1$, $F(2,37) = 1.2$, $p = 0.15$). This was not surprising given that the relationship between misattribution and individual differences was expected to vary as a function of condition (action-outcome discordance).

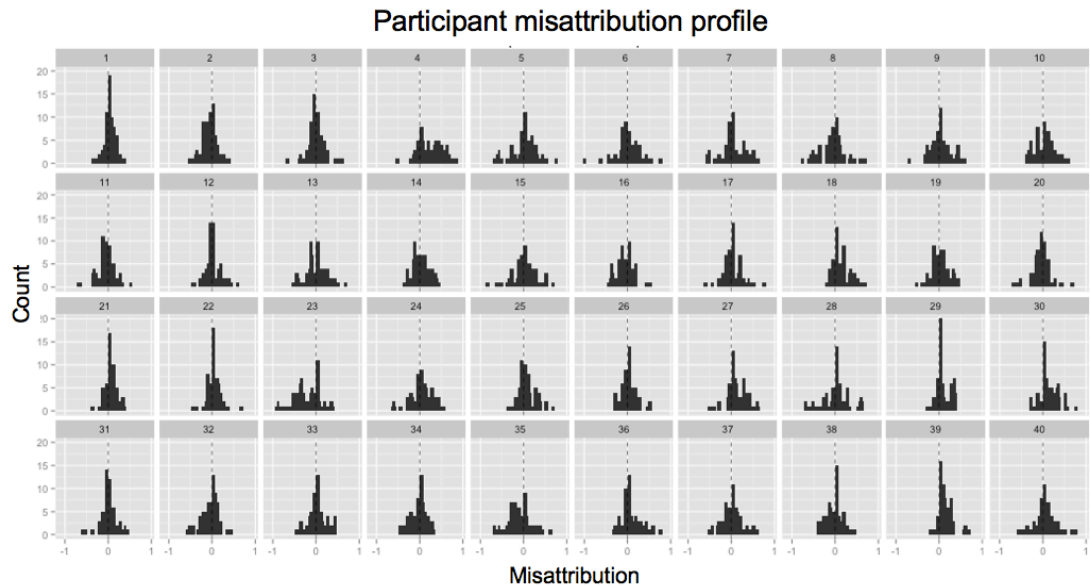


Fig. 2.3. Participants' distribution of misattribution (difference between attribution ratings and condition) with data pooled over all conditions.

2.4.3. Misattribution as a function of condition

As a preliminary investigation of the data, linear regressors were first used to describe each individual's misattribution as a function of condition (discordance). A higher-level regression was then conducted to examine whether individual differences were related to resulting slopes (beta coefficients). As may be seen in Table 2.3, both HP and ME were significant predictors of slope, pointing in opposite directions. A t-test comparing r-squared (R^2) values, revealed that misattribution was better characterised ($t(77.53) = -4.7694, p < .0001$) as a quadratic (mean $R^2 = .59$) rather than a purely linear function (mean $R^2 = 0.42$). Both linear and quadratic slopes were significant predictors of HP. Similarly, ME was predicted by linear and quadratic slopes which again pointed in the opposite direction. The fit of the quadratic model to the data (R^2) was also positively related to HP and negatively related to ME, suggesting that misattribution as a function of condition was more quadratic in high HP and low ME. Fig. 2.4 shows that misattribution biased towards other (positive values) peaks around condition 4 while misattribution biased towards self (negative values) peaks at condition 10. For visualisation purpose only, the data has been split between high and low HP and high and low ME to show that this trend (described as positive or negative distance from 0 – an errorless attribution score) is

particularly pronounce in individuals with high HP (Fig. 2.4a) and low ME (Fig. 2.4b).

Table 2.3. Two-step regressions for 40 participants (M = misattribution; C = condition; C^2 = quadratic term of condition; HP = hallucination proneness; ME = musical experience; β = slope; R^2 = r-squared; \sim = predicted by) Step 1 shows the regression fitted on each participant separately; step 2 shows the models fitted at group level (df = 2, 37 in all four models).

	Model 1	Model 2	Model 3	Model 4
Step 1	M \sim C	M \sim C+C ²	M \sim C+C ²	M \sim C+C ²
Step 2	(C β \sim HP+ME)	(HP \sim C β +C ² β)	(ME \sim C β +C ² β)	(R ² \sim HP+ME)
(Intercept)	-0.02 ^{***} (0.006)	4.25 (2.35)	13.34 ^{***} (2.45)	0.19 ^{***} (0.04)
HP	-0.0008 [*] (0.0003)			0.006 [*] (0.002)
ME	0.0007 [*] (0.0003)			-0.005 (0.002)
C β		-158.21 [*] (63.84)	152.48 [*] (66.39)	
C ² β		-2215.88 ^{**} (704.98)	1893.45 [*] (733.23)	
R ²	0.25	0.27	0.16	0.24
Adj. R ²	0.21	0.23	0.12	0.22
Num. obs.	40	40	40	40

*** p < 0.001, ** p < 0.01, * p < 0.05

Statistical models

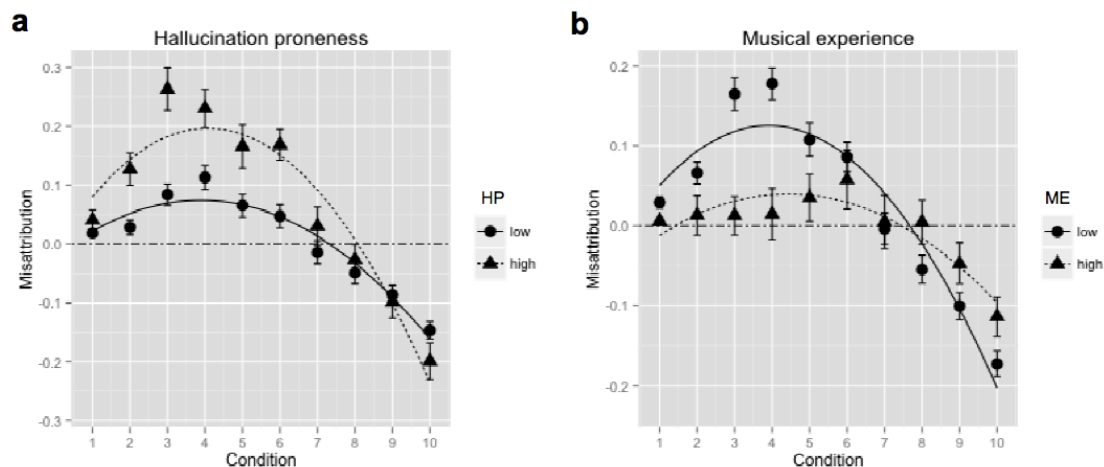


Fig. 2.4 (a,b). Misattribution as a function of condition for low and high HP (a) and low and high (b) ME. Error bars represent standard error of the mean.

A multilevel approach was considered to be more appropriate for this data and for the action attribution phenomena being explored. This analysis, conducted using the lme4 library in R, not only allowed trials to be nested within participants, but also

enabled misattribution to be investigated as a quadratic function of discordance in relation to individual differences within the same model (Goldstein, 1995; Snijders & Bosker, 1999). In contrast to two-step regressions, participant slopes were weighted by their standard error, as multilevel models use information from the whole sample data when making estimates for any one participant. This makes estimates more reliable and inferences generalizable to the population (Richter, 2006; Goldstein, 1995). All predictors were mean centered in accordance with previously used procedures (e.g., Rasbash et al., 2000) and both the intercept and slope were allowed to vary between participants.

Confirming our previous results, the multilevel analyses showed that a linear and quadratic effect of condition significantly predicted misattribution (Table 2.4). Misattribution was found to increased with HP and decreased with ME when they were added as main effects. Including two-way interactions into the model revealed a negative relationship between condition and HP and a positive relationship between condition and ME. The R package visreg, version 2.0-4 (Breheny & Burchett, 2012) was used to visualise interaction effects by inputting the model's predicted values. 2.5 not only confirms that positive misattribution (a bias towards other; shown in dark red) peaked in more ambiguous conditions (between C3 and C4), but also that it was in these conditions that HP and ME best predicted misattribution (Fig 5 a and 5b). HP predicted increased misattribution towards other while ME was associated with attenuated misattribution towards other. A negative interaction between HP and ME was also found to be significant. As Fig 5c shows, misattribution to be associated with high HP and low ME while low misattribution (an errorless score of 0) were associated with low HP and high ME.

Table 2.4. Multi-level models predicting misattribution for 40 participants. The first section shows the slope (β) and bootstrapped 95% confidence interval (CI) for the fixed part of the model, including main effects and two-way interactions between condition (C), the quadratic term of condition (C^2), hallucination proneness (HP), and musical experience (ME). The second section shows between-subject variance in intercept, residual, and condition). The third shows the model fit (using Bayesian information criterion (BIC)) and the number of observations and groups (participants).

	(Intercept)	C	C^2	HP	ME	C:HP	C:ME	HP:ME
β	0.0829*	-0.0244*	-0.0079*	0.0041*	-0.0031*	-0.0008*	0.0007*	-0.0006*
95 % CI	[0.0583; 0.1075]	[-0.03; -0.0188]	[-0.0092; -0.0067]	[0.0014; 0.0068]	[-0.006; -0.0003]	[-0.001; -0.0001]	[0.0001; 0.0013]	[-0.0011; -0.0001]
Variance: Subject.(Intercept) = 0.004; Variance: Residual = 0.0406; Variance: Subject.Condition: 0.0001								
BIC = -557 ; Num. obs. = 2021; Num. groups = 40								

* 0 outside the confidence interval

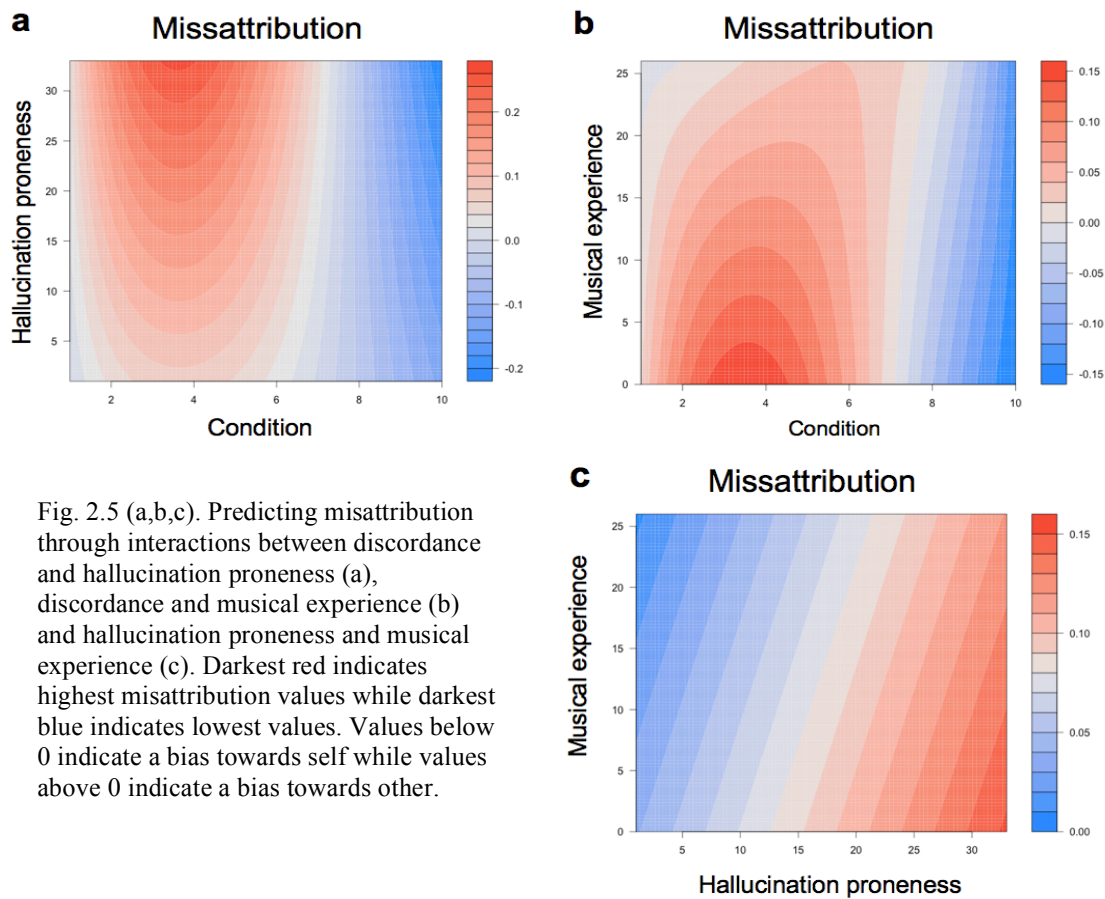


Fig. 2.5 (a,b,c). Predicting misattribution through interactions between discordance and hallucination proneness (a), discordance and musical experience (b) and hallucination proneness and musical experience (c). Darkest red indicates highest misattribution values while darkest blue indicates lowest values. Values below 0 indicate a bias towards self while values above 0 indicate a bias towards other.

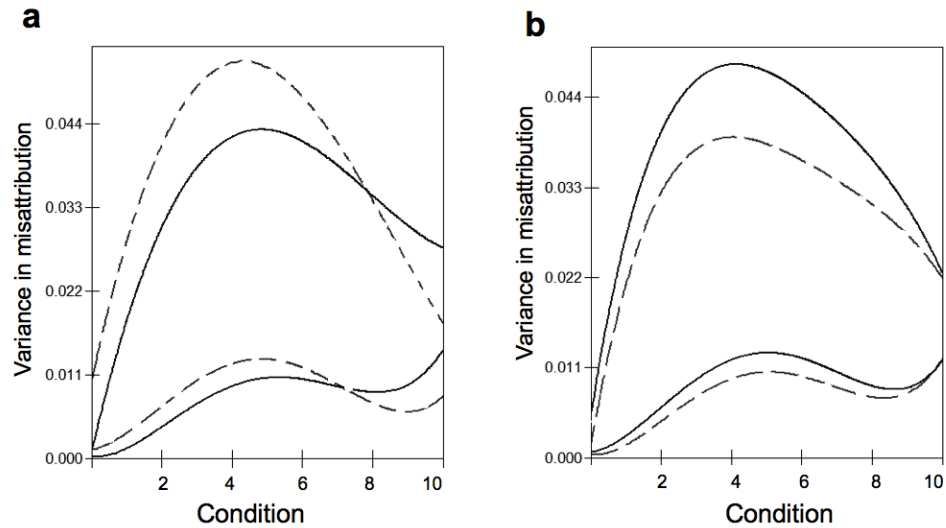


Fig. 2.6 (a,b). Variance within-individuals (level 1) as a function of condition (discordance) is shown in the top 2 lines of both (a) and (b) while the bottom two lines in both graphs represent between-individual (level 2) variance. Full lines indicate low HP in (a) and low ME in (b), while dashed lines represent high HP in (a) and high ME in (b).

To visualise the variability in our model, variance at both within- and between-individual levels were plotted as a function of condition (discordance) using MLwiN version 2.10. Fig. 2.6 shows that, in addition to being biased towards other, participants' misattribution tended to be more random (varied) in the middle of the self-to-other continuum (two top lines in Fig. 2.6a and 2.6b). This pattern was accentuated by high HP (depicted by the dashed line in Fig. 2.6a) and low ME (depicted by the full line in Fig. 2.6b), in line with the analysis predicting variance in misattribution (SD) over all conditions with individual differences. Misattribution variance between-individuals (lower lines in Fig. 2.6a and 2.6b) shows a general positive trend, with peaks in the middle and at the end of the continuum.

2.5. Discussion

This study investigated misattribution across a self-to-other continuum in healthy participants, examining individual differences thought to be associated with lower (HP) and higher action attribution abilities (ME). Participants engaged in a button-press task resulting in auditory tones. Ten conditions – parametrically manipulating the probability that an action of self versus other would generate a tone – were used

to obtain a systematic measure of action-outcome discordance.

In line with behavioural and imaging findings showing that action attribution to self and other is processed in a continuous manner (e.g., Farrer et al., 2003; Franck et al., 2001; Sato & Yasuda, 2005; Fukushima et al., 2013), results revealed that the continuous measure of discordance was a better predictor of participant's attribution ratings than a binary measure. The quadratic finding showing that misattribution (Fig. 2.4 and 3.5) and its variability within individuals (Fig. 2.6) was greatest near the middle of the discordance continuum supports the view that ambiguity plays an important role in agency (Fukushima et al., 2013; Gallagher, in press). It suggests that individuals' ability to attribute actions to self and other is markedly diminished in ambiguous contexts. Using a parametric fMRI design (Buchel et al., 1998), future research using the task developed here will explore how particular brain regions respond to this type of ambiguity.

The general direction of misattribution in the middle of the discordance continuum was towards other rather than self for all participants. While this accords with the majority of phenomenological and clinical accounts in schizophrenia that describe the loss of control over self-generated thoughts or actions, some studies have also shown a bias towards self in healthy subjects (Repp & Knoblich, 2007) and people with schizophrenia (Daprati et al., 1997; Franck et al., 2001) that could reflect a cognitive coping mechanism for dealing with distressing ambiguous situations – an attempt to regain control over self (see Hauser et al., 2011). This explanation also fits with the idea that direction of bias is dynamic, changing in response to psychopathological development and possibly mediated by progressive degradation of glutamatergic pathways (Moore & Obhi, 2012). Our findings demonstrate that the direction of misattribution reverses from other to self by the end to the continuum for all participants (Fig. 2.4 and 2.5). It seems likely, therefore, that discrepancies in the literature may be due to task differences between studies in the calibration of the 'other' condition and, more specifically, the amount of discordance associated with other in the different paradigms.

Other task and stimulus characteristics are also likely to play a part in the direction that misattribution takes. For example, consistent with evidence for a self-serving

bias (Campbell & Sedikides, 1999), an aversive task or stimulus could be expected to promote a bias towards other while a rewarding task/stimulus may promote a bias towards self (e.g., An et al., 2010; Federoff & Harvey, 1976). Research shows that attention is also likely to be a determining factor. Individuals primed to attend to themselves are more likely to display a bias towards self (Duval et al., 1979), while a bias towards other individuals or groups is more likely when attention is drawn towards these entities (Lassiter et al., 2002; Taylor and Fiske, 1978). The fact that a bias towards other was observed in most participants (irrespective of HP and ME) using a neutral task involving low-level temporal cues suggests that, when faced with ambiguity, self is (by default) experienced as having less control over events in the world than it actually has. Future work could manipulate factors such as task or stimulus valence, attentional cues, participants' subjective states (e.g., anxiety level), and the relation that self has with other (e.g., friend/foe; human/computer) to examine how such factors interact with the extent, direction and variance of misattribution.

Our findings also suggest that HP is associated with increased misattribution towards other (when controlling for the effects of discordance), as well as greater overall variance in misattribution (SD of misattribution over all conditions), confirming previous findings that associate dysfunctional action monitoring with passivity phenomena and schizotypal personality traits (Daprati et al., 1997; Fournier et al., 2001; Knoblich et al., 2004; Asai et al., 2008). In contrast, reduced bias towards other and less misattribution variance was related to ME. This suggests that musical experience makes individuals more reliable at judging the proportion of control belonging to self and other, at least in the auditory domain. Supported by findings that musicians have more pronounced auditory and motor system coupling (Zatorre et al., 2007) and use sensorimotor cues effectively in action attribution (Knoblich & Repp, 2009), music-making may improve predictions of self-generated outcomes. However, action attribution style is also likely to be determined by the accuracy of predictions made for others' actions and for the combined actions of both self and other (Pacherie, 2011), which is likely to develop through experience in intricate joint action.

Again, it was in ambiguous conditions that the observed effects of HP and ME on misattribution were most pronounced. HP correlated with increased misattribution towards other (Fig. 2.5a) as well as increased variability (Fig. 2.6a) in the middle of the self-to-other continuum. The latter fits with research associating psychotic symptoms of schizophrenia to the formation of indiscriminate (noisy) action-outcome associations and predictions (Moore & Obhi, 2012). Findings that link delusions to a tendency to jump to conclusions in uncertain situations (Linney et al., 1998; Van Dael et al., 2006) and an inability to tolerate ambiguity (Colbert & Peters, 2002; Grube, 2002) support the fundamental role of ambiguity as a trigger for psychotic-like experiences. There is also, of course, robust and widespread evidence for poor performance on diverse information processing tasks in schizophrenia (Potkin et al., 2009) including salience processing (Kapur, 2003; Walter et al. 2010) and attention (Tyson et al., 2008) – skills that are likely to mediate the detection and resolution of conflicting information. Interestingly, these skills have also been related to impaired social functioning (Cohen et al., 2006:236). Building on work identifying theory of mind (ToM) difficulties in schizophrenia (Corcoran, 2000; Brune 2003), research has more recently focused more generally on social cognition (Biedermann et al., 2012; Mier et al. 2010; Walter et al., 2010) and between-individual interaction (Liepelt et al., 2012; Trognon, 1992; Wan et al., 2008.).

Frith (1992) among others has argued that such cognitive deficits and the unusual beliefs that are a core feature of schizophrenic delusions are rooted in a lower-level self-monitoring impairment. Our findings put forward the argument that socio-cognitive difficulties may be underpinned by misattribution during the processing of causal ambiguity within social contexts. Notably, only inductive information processing can help within characteristically ambiguous social situations because deductive processes rely on definitive information (Corcoran et al., 2006; Bennett & Corcoran, 2010). Ambiguity drives a hunt for disambiguating information (Gibson, 1966:303) from the internal or external environment. These are the very reality-testing reflexes that may be dysfunctional in individuals experiencing psychosis (e.g., Aggemaes, 1972; Moritz & Woodward, 2006). Future research could examine individual differences in information-seeking strategies within ambiguous contexts.

Finally, the association found between ME and attenuated misattribution and

variance within-individuals was also most pronounced in ambiguous conditions. This finding resonates with those demonstrating that long-term music training is related to improvements in working memory (e.g., George & Cock, 2011) and other higher order cognitive skills that involve simultaneous processing of information and attentional control (e.g., Lee et al., 2007; Helmbold et al., 2005; Moreno & Besson, 2006). Longitudinal studies have also shown that such improvements are more likely to result from musical training rather than from any innate musical predisposition (e.g., Lahav et al., 2007; Hyde et al., 2009; Moreno et al., 2009). Experience-induced improvements in executive function have also been observed outside the domain of music (Hussey et al., 2012; Manly & Murphy, 2012). For example, individuals with Tourette's syndrome have shown enhanced cognitive control on executive function tests which may be explained by the constant effort exerted to suppress tics when in public (Mueller et al., 2006). This finding is consistent with an increased need to monitor and control movements and may indicate a subcortical locus for the triggering of tics. It also suggests that the constant need to suppress tics could have resulted in an enhancement of the executive processes involved in inhibitory control. Music therapy findings also show improvement in patients with positive symptoms (Silverman, 2003; Peng et al., 2010; Na & Yang, 2009). This research, alongside our finding of an interaction between HP and ME (Fig. 2.5c), supports the view that attribution abilities are malleable. It also leaves open the possibility that engagement in intricate joint-action from an early age is what enables individuals to learn to differentiate self from other in ambiguous contexts.

Whether increasing attribution accuracy in ambiguous contexts is possible through experience in particular activities and whether this would alleviate distressing symptoms of psychosis are open questions. However, given the findings presented here, research directly comparing behavioural and neural differences between individuals with passivity-related phenomena and expert joint-actors such as musicians is justified.

2.6. Summary and conclusions

Results from this study support previous findings that show action attribution to be continuous rather than categorical and stresses the central role that ambiguity plays in action attribution and agency. The study confirms the link between action attribution deficiencies, passivity-related phenomena and schizotypal traits. However, these are the first experimental findings to suggest that such deficiencies may be related to an impairment in processing causal ambiguity between self and other. Data showing ME to be associated with reduced misattribution within ambiguous contexts suggest that action attribution style may be malleable, and that extensive experience in joint-action could improve attribution abilities. Finally, the important clinical question of whether experience-based improvement in action attribution can lead to a reduction of passivity symptoms is a worthwhile avenue for future investigation.

2.7. Acknowledgements

The authors would like to thank the Institute of Psychology Health and Society, University of Liverpool for funding data collection and a studentship.

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CHAPTER 3

Neural response to modulating the probability that actions of self or other result in auditory tones: A parametric fMRI study into causal ambiguity.

[de Bézenac, C. E., Sluming, V., Gouws, A., & Corcoran, R. (2016). Neural response to modulating the probability that actions of self or other result in auditory tones: A parametric fMRI study into causal ambiguity. *Biological Psychology*, 119, 64-78.]

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3.1. Abstract

In normal circumstances we can easily distinguish between changes to the external world brought about by our own actions from those with external causes. However, in certain contexts our sense of ownership and agency over acts is not so clear. Neuroimaging studies have implicated a number of regions in the sense of agency, some of which have been shown to vary continuously with action-outcome discordance. However, little is known about dynamic, ambiguous contexts characterised by a lack of information for self-other differentiation, yet such ambiguous states are important in relation to symptoms and levels of consciousness that characterise certain mental health conditions. With a block-design fMRI

paradigm, we investigated neural responses to changes in the probability that a participant's irregular finger taps over 12 sec would result in auditory tones as opposed to tones generated by 'another's finger taps'. The main findings were that misattribution increased in ambiguous conditions where the probability of a tone belonging to self and other was equal. Task-sensitive brain regions, previously identified in self-agency, motor cognition, and ambiguity processing, showed a quadratic response to our self-to-other manipulation, with particular sensitivity to self-control. Task performance (low error and bias) was related to attenuated response in ambiguous conditions while increased response in regions associated with the default mode network was associated with greater overall error and bias towards other. These findings suggest that causal ambiguity as it occurs over time is a prominent feature in sense of agency, one that may eventually contribute to a more comprehensive understanding of positive symptoms of psychosis.

Keywords: Parametric design; fMRI; agency; causal ambiguity; self and other; prediction error

Highlights

- A parametric agency task manipulating the probability of self-other control
- Misattribution increased in ambiguous conditions
- Task-modulated regions showed a quadratic response most sensitive to self-control
- Task performance predicted attenuated response in ambiguous conditions
- Overall error and bias towards other predicted increased response in DMN nodes

3.2. Introduction

The ability to make accurate predictions about the underlying causes of sensory input is one of the primary tasks of the brain (Friston et al., 2010; Clark, A., 2013). In normal circumstances we automatically distinguish between changes to the external world brought about by our own actions from those with external causes. Agency – the sense of being the cause – is a multifaceted phenomenon, involving somatosensory signals, body schema, and also higher-order intentions, goals and desires (Gallagher, 2000; Synofzik, Vosgerau & Newen, 2008). The comparator model proposes that sensory input that matches our prior intention or action (low prediction error) is experienced as self-generated, while a discrepancy (high prediction error) is more likely to be attributed to an external cause, such as another agent in the vicinity (Frith, 2005; Wegner, 2002; Von Holst, 1954). This prediction error mechanism, also observed at a sensorimotor level in non-humans (Bell, 2001; Poulet & Hedwig, 2002), is well supported by empirical work that manipulates the predictability of action consequences. For example, a number of paradigms use temporal delay or spatial displacement to distort the results of a participant's action in visual, tactile, or auditory stimuli (Blakemore, Wolpert, & Frith, 1998a; Farrer et al., 2003; Lindner et al., 2005; Synofzik, Thier, & Lindner, 2006; Sato & Yasuda, 2005).

Neuroimaging research has implicated several brain regions in the attribution of actions to self and other and the associated sense of agency. These include areas known to be involved in sensorimotor processing and motor control such as the ventral premotor cortex (Kaplan & Iacoboni, 2007), the putamen (David et al., 2007), the supplementary motor area (SMA) (Cunnington et al., 2006; Lau et al., 2004) and cerebellum (Blakemore & Sirigu, 2003; Agnew & Wise, 2008). Multi-modal regions involved in temporal aspects of cognition have also been implicated (Voeley & Kupke, 2007), including the posterior parietal cortex (PPC) and inferior parietal lobe (IPL) (Farrer et al., 2003; 2008; Agnew & Wise, 2008; Fink et al., 1999), the dorso and ventral lateral prefrontal cortex (DLPFC; VLPFC) (Fink et al., 1999; Schnell et al., 2007; David et al., 2007), the posterior segment of the superior temporal sulcus (pSTS) (Ramnani & Mial, 2004; Spengler et al., 2009), and the insula (Farrer et al., 2002; 2003) (for reviews see: Sperduti et al., 2011; David et al., 2008).

While the exact function of these regions in agency processing remains unclear, with contradictory evidence in some cases, on the whole it is thought that action attribution to self and other is supported by partially distinct neural substrates (Sperduti et al., 2011). Increased activity in the PPC and IPL, for example, has tended to be linked to the attribution of action to external causes and to sensorimotor mismatch (Moore et al., 2010; Farrer et al., 2003; McGuire et al., 1996; Spence et al., 1997; Ruby and Decety 2001; Farrer and Frith, 2002), while the putamen, insula, cerebellum, and SMA have been associated with attributing intentions and actions to self (Farrer & Frith, 2002; David et al., 2007; Haggard & Whitford, 2004; Lau et al., 2004; Farrer et al., 2003; Leube et al., 2003).

However, typically agentic decision-making does not involve information that clearly distinguishes self from other. Some studies have used experimental manipulations that allow intermediate conditions to be represented (Franck et al., 2002; Sato & Yasuda, 2005; Blakemore et al., 1998; Farrer et al., 2003). For example, in a PET study that manipulated the angular distortion of visual feedback, Farrer et al., (2003; 2004) found that the degree of a subject's control over action outcomes modulated brain activity *continuously*, with the insula and cerebellum decreasing and the IPL and preSMA increasing with loss of control. That the sense or judgement of agency is a question of degree makes sense given that discrepancy between action and outcome (prediction error) can range from high to low with sensorimotor cues (e.g., timing between action and feedback) also varying in a continuous rather than a categorical manner.

It is in ambiguous contexts where control over sensory outcomes belongs neither fully to self nor to other that agency is likely to be most challenged (de Bezenac et al., 2015). Take, for example, a situation where two or more individuals play a mutual game (e.g., Ouija board; Ansfield & Wegner, 1996). As the sensory input is co-produced and the mutually coordinated actions of self and other produce similar outcomes, it may be difficult for us to know whether an event is caused by self or by another participant (Wegner & Wheatley, 1999). Information for self-other differentiation is reduced making misattributions more likely: we may feel that others have control over events that in fact belong to self (bias towards other); or that

self has control over outcomes resulting from the action of others (a bias towards self). Though causal misattributions of this sort have been associated with phenomena such as delusions of control and auditory verbal hallucinations (Spence et al., 1997; Parnas & Handest, 2003; Jeannerod, 2009; Ditman & Kuperberg, 2005; Lindner et al., 2005; Frith, 2005; Woodruff, 2004), they are also characteristic features of complex social encounters, where the actions, intentions and resulting outcomes of participating individuals are matched, parallel and intricately comingled. However, despite its ubiquitous nature and potential relevance to disorders characterised by the blurring of self-other boundaries, still little is known about the role that ambiguity plays in causal attribution and how the brain responds to situations with reduced information for self-other differentiation.

In a recent study, Fukushima et al., (2013) used a paradigm that adjusted delay between action and visual feedback to make agency maximally ambiguous for each individual. They found that attribution in such contexts was associated with activity in temporo-parietal areas (IPL, TPJ), medial frontal areas (SMA, ACC), the DLPFC, and frontal operculum/insula regions, while activity in posterior midline areas (PCC; precuneus) specifically correlated with self-attribution. Outside the domain of agency-focussed research, ambiguity has been studied as a key dimension of everyday experience that significantly influences decision-making and behaviour (Yoshida and Ishii, 2006). Imaging research on the topic has also implicated the DLPFC (Huettel et al., 2005), associated with conflict resolution (Mansouri et al., 2009), the IPL (Britz et al., 2009; Volz et al., 2003), the ACC (Botvinick et al., 2001; Stern et al., 2010; Critchley et al., 2001), an area thought to be involved in conflict detection (Carter et al., 2007) (for a review see, Krain et al., 2006), as well as the amygdala (Hsu et al., 2005; Zaretsky et al., 2010). That these regions (apart from the amygdala) have also been shown to be responsive to agency-related tasks supports the role of active ambiguity processing in agency.

The ability to tolerate ambiguity has also been implicated in a range of psychopathological disorders including general anxiety disorder (Buhr & Dugas, 2002), obsessive-compulsive disorder (Tolin, Woods, & Abramowitz, 2003), and schizophrenia (Broome et al., 2007). Understanding the relationship between

ambiguity and agency may therefore contribute to a more comprehensive conceptualisation of positive symptoms of psychosis.

There are methodological challenges associated with examining how the brain responds to causal ambiguity. For example Fukushima et al.'s (2013) elegant study was limited by the fact that the paradigm did not allow neural response for ambiguous and non-ambiguous conditions to be compared. As the authors indicated, this could be achieved by parametrically varying the degree of ambiguity. In the continuous manipulation used by Farrer et al. (2003), differences between the 4 successive conditions were not likely to be equal/systematic, as they included: (1) undistorted feedback (self); (2 and 3) varying degrees of feedback distortion (angular bias of 25 and 50 degrees, respectively); and (4) the outcome of the experimenter's movement. Furthermore, a feedback distortion approach may be susceptible to adaptation confounds, with participant's eventually recognizing themselves in non-manipulated aspects of the stimuli (e.g., movement velocity) (Honda et al., 2012; Cunningham et al., 2001). It is also not obvious how much action-outcome discrepancy is required for a stimulus to be experienced as ambiguous or as belonging to other. Studies using such paradigms have therefore tended to rely on participant's subjective attribution rating given as a categorical rather than continuous response (action of self: yes/no). Ideally, behavioural and brain response would be measured against an objective and systematic continuum ranging from control belonging fully to self, to control belonging fully to other, with ambiguity peaking in the middle.

But what does the middle of a self-to-other continuum look, feel or sound like, and in what ways can information for self-other differentiation be reduced? According to Rimmon (1977), ambiguity emerges from a balanced system of conflicting cues. These cues can be balanced by pointing towards alternative interpretations (e.g., self/other) *simultaneously or sequentially*. By directly manipulating the degree of action-outcome discrepancy in distortion paradigms, keeping it constant within conditions, previous agency research has focused primarily on the former. In reality however, an event is processed in the context of other events that vary in action-outcome discrepancy over time, pointing towards self one moment and other the

next. In dynamic social contexts outside experimental settings, the sense of agency is therefore likely to involve the weighing up and monitoring of successive stimuli, updating and averaging prediction error over a given period of time. In addition to previously mentioned agency-related brain regions, this may be expected to implicate networks associated with motor planning and adaptive learning that involve executive function and working memory (Apps & Tsakiris, 2014; Nieoullon, 2002). A clearer understanding of how overall proportion of stimuli caused by self versus other is processed and experienced may help fill a gap that exists between research examining agency as it functions in different temporalities, ranging from sensorimotor processes operating primarily at smaller timescales, to the overall control that a person feels over their lives, which involves attribution averaged over larger timescales (Gallagher, 2013). From this perspective, causal ambiguity may be objectively defined: it emerges when the proportion of control over stimuli is equally distributed between self and other over a given period of time. This situation can arise when action-outcome discrepancy is neither high nor low and when it fluctuates between the two to an equal extent. In either setting, the information available for self-other differentiation is limited.

The aim of this study was therefore to examine brain response to the proportion of control belonging to self in relation to other, with a particular focus on ambiguous situations where action outcomes do not exclusively belong to self or to other but to varying mixtures of both. To examine this, we used a tapping task developed in our lab (de Bezenac et al., 2015). In this task participants perform irregular self-paced taps for a duration of 12 seconds whilst listening to a sequence of tones. Rather than directly manipulating action-feedback discrepancy (as previous paradigms have done), we varied the probability that self-produced finger taps would result in auditory tones as opposed to taps belonging to ‘other’ (made up of randomised taps of self). This was done in 5 equal steps (conditions 1 to 5). Highest tap-tone synchrony occurred in condition 1 (C1) where probability was equal to 1 for self and 0 for other, while maximal discordance occurred when probability was 0 for self and 1 for other. Ambiguity peaked in the middle of the self-to-other continuum (C3) where tones were as likely to belong to self as to other (self=0.5; other=0.5), in random fluctuation.

Neural response to this self-to-other manipulation was tested in a parametric block design, taking advantage of its greater statistical power compared to event-related designs (Friston et al., 1999). Parametric designs have previously been used to investigate the specific roles that regions play in a given process (Cohen et al., 1997, Rees et al., 1997; Schlaug et al., 1996), avoiding some of the pitfalls associated with subtraction logic (Donders, 1969). After identifying regions showing significant response variation across conditions (in a whole brain group analysis), we used linear and non-linear regressors to characterise stimulus-response functions (Büchel et al., 1998). The shape of the BOLD response has implications for the role played by identified regions in differentiating action outcomes belonging to self from those belonging to other.

More specifically, regions previously identified as being associated with control belonging to self were expected to show an increased response as the likelihood of self-produced tones increased (a negative linear trend in relation to conditions 1-5). Regions previously identified as being sensitive to the actions of other were expected to increase as the proportion of tones belonging to other increased (a positive linear trend in relation to conditions 1 -5). A significant quadratic response was interpreted as sensitivity to causal ambiguity, indicating either a reduced or increased response near the middle (compared to the extremes) of the self-to-other continuum. Subjective attribution responses were also collected after each trial, allowing the function of identified regions to be further investigated using task performance measures. Given that (i) a paradigm allowing variation of self-other control within trials has not yet been used in an imaging study and (ii) the function of brain regions in agency is still unclear, we used conservative Z thresholds, whole-brain multiple comparison correction, and examined/presented stimulus-response functions in all significant regions rather than selecting them on the basis of a priori hypotheses. Thus, the aims of the study were 3-fold: (1) to identify brain regions responding to the proportion of self-other control over action outcomes, (2) to distinguish linear and nonlinear brain responses in these regions, and (3) to examine how response varied in relation to task performance.

3.3. Methods

3.3.1. Participants

Twenty-four healthy right-handed student volunteers (12 male, 12 female) took part in this study (age: $M = 32.3$, $SD = 8.4$). Participants had no previous history of mental illness or neurological abnormalities and reported the absence of difficulties in auditory, visual and somatosensory perception. The study was approved by the ethics committee of the University of Liverpool and conducted in accordance with committee policies.

3.3.2. Experiment stimuli

Audio-visual stimulus presentation and participant response collection were managed using Pure Data (Puckette, 1996: <http://puredata.info/>). In the scanner, participants completed the behavioural task using an MRI-compatible response box with instructions provided visually via a projector screen seen through inverting mirrors. Auditory stimuli were presented diotically through pneumatic tubes within the ear protector at a volume of 95 dB and consisted of a tone with the following parameters: cosine wave, 262 Hz; 100 ms duration; 20 ms onset ramp; 5 ms offset ramp. This tone could be triggered by one of the three keys of the response box positioned on the participant's right thigh. All participants reported that the tone could be clearly heard during data acquisition, following finger taps without perceptible delay (inherent delay = 25ms).

Tones could either result from the participant's own actions (self) or from the actions of another individual (other). To ensure that stimuli were similar within participants and conditions, taps produced by other actually consisted of the participant's own 50 previous intertap intervals played back in a random order. The probability that a tap belonging to self would result in a tone (as opposed to one belonging to other) was manipulated in five equal steps, corresponding to the five experimental conditions (C) ($C1 = \text{probability of } 1$, $C2 = .75$, $C3 = .5$, $C4 = .25$, $C5 = 0$). Probability manipulation was achieved by generating a random number between 0 and 1 every time a self or other tap occurred. Each condition was associated with a threshold above which tones generated by self would be heard and below which tones generated by other would be heard. In condition 1, the threshold was set to 1,

meaning that all tones were self-generated (maximal tap-tone synchrony). In contrast, as condition 5 had a threshold of 0, all tones belonged to other (maximal tap-tone discordance). A threshold of .5 resulted in control being equally distributed, shifting between self and other (semi-discordance). Conditions 2 and 4 were allocated thresholds of .75 and .25, respectively. Fig. 3.1 provides an example of the result of the probability manipulation where temporal relationships between auditory tone onsets and self/other-generated taps are depicted as a series of peaks. Note that peaks in top lines (red), which represent a participant's irregular taps (Self), are synchronised with tones heard in condition 1 (top line peaks meet middle line peaks), semi-synchronised in condition 3, and asynchronised in condition 5.

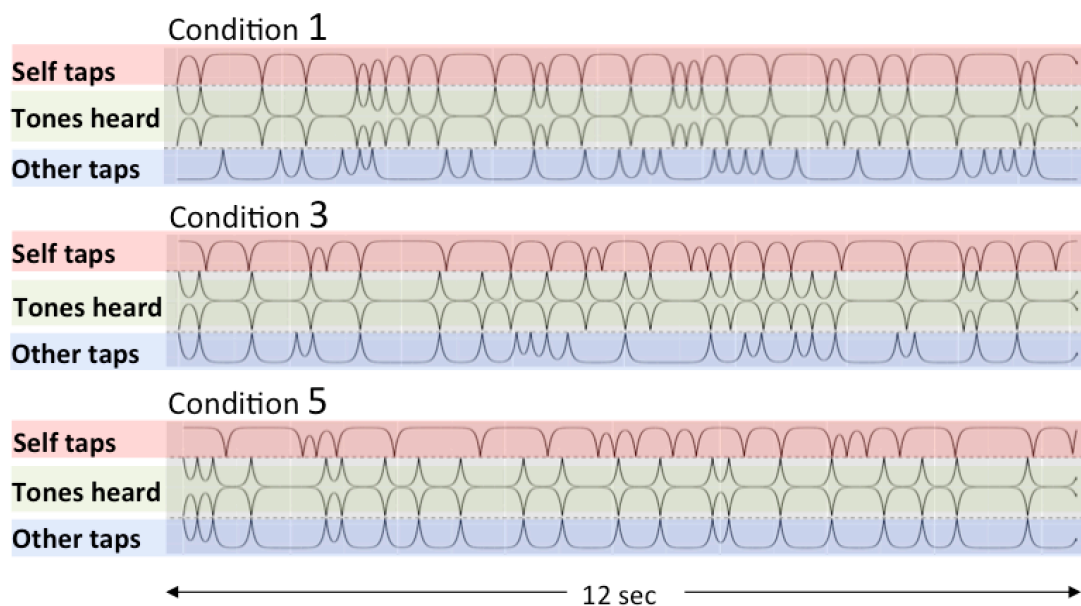


Fig. 3.1. Temporal relationships between self-produced taps (red), tone heard (green), and taps of other (blue). Data shown are from one arbitrarily chosen participant from a pilot study in conditions equivalent to 1 (self fully in control), 3 (ambiguous control: the probability that self or other will produce a tone is equal), and 5 (other fully in control). Peaks in top lines (which represent the participant's irregular taps), are synchronised with tones heard in condition 1 (peaks meet), semi-synchronised in condition 3, and asynchronised in condition 5.

3.3.3. Imaging parameters

Scanning was performed at the Magnetic Resonance And Image Analysis Research Centre (MARIARC), University of Liverpool with a Siemens Trio 3.0 Tesla (Siemens, Erlangen, Germany), whole body MRI system, equipped with an eight-channel phased array head coil. Foam padding and head restraints were used to minimise head movement during imaging. For fMRI scanning, echo-planar images were acquired using a T2* weighted gradient echo sequence with blood oxygen level dependent (BOLD) contrast (TR = 3000 ms; TE = 30 ms; flip angle = 90°, 49 slices,

distance factor = 10 mm, interleaved multi-slice mode, matrix = 64 x 64; FOV = 192 mm; acquisition voxel size = 2.7 mm³). Each experimental scan consisted of 197 contiguous EPI functional whole head volumes. Before preprocessing these functional data, the first eight volumes of each run were automatically removed to allow for magnetic stabilization. T1-weighted MR images were acquired sagittally for each participant with the following parameters: TE 5.57ms, TR 2040 ms, flip angle 8°, FOV=256×256 mm², 176 slices, voxel size 1×1×1 mm³.

3.3.4. Experimental scan

Participants were asked to perform series of irregular taps (“like Morse code”) using their right index finger whilst listening to a sequence of tones. A recorded example of tapping was provided and a practice session outside the scanner ensured that tap density was similar across participants and conditions. They were told that tones could either result from their own actions (self) or from the actions of another individual (referred to as ‘other’), and that the proportion tones belonging to self or other would vary between trials. Experimental blocks consisted of 12 seconds of tapping, indicated on the screen by the word “Play”. After each block, participants were given 5 seconds to report the proportion of control that they felt belonged to self or other along a continuum represented by a rectangular box within which a vertical bar appeared in a randomised initial position. Using the two remaining keys of the response box, participants were able to move that bar towards self (left) or other (right) to represent the locus of experienced control. The rating period was followed by a 6 second fixation cross (jittered by up to 2 seconds) to ensure that BOLD response returned to baseline levels, including a 3 digit countdown to the start of the following block (500 ms per digit). Each of the 5 conditions was repeated 10 times and presented to participants in a pseudo-random order, with the constraint that consecutive conditions were not presented in consecutive blocks. The 50 blocks were divided into two 12-minute scans (25 blocks in each). A schematic representation of the experimental paradigm is provided in Fig. 3.2. Participants also underwent a T1/T2 structural, resting-state and DTI scan, meaning that scanning sessions were approximately 50 minutes long.

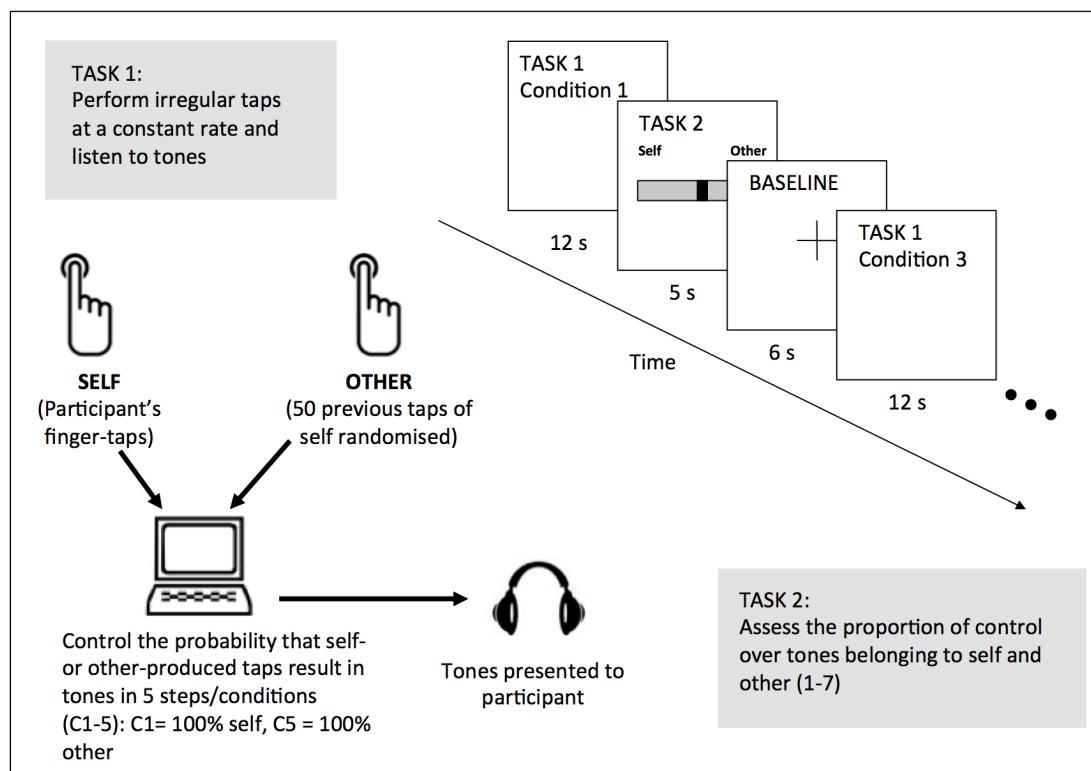


Fig. 3.2. Schematic representation of the experimental paradigm.

3.3.5. *fMRI data analysis*

Image analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). For each participant the following pre-statistic processing was applied: motion correction using MCFLIRT (Jenkinson, 2002); slice-timing correction using Fourier-space time-series phase-shifting; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma=45.0s$). ICA-based exploratory data analysis was carried out using MELODIC (Beckmann, 2004), in order to investigate the possible presence of unexpected artefacts or activation. Following pre-statistics processing, a time series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001).

The general linear model (GLM) design matrix for the two experimental scans had one explanatory variable per condition that was "on" during corresponding blocks

and "off" elsewhere. Parameter estimates (PE) were calculated for each explanatory variable using a double-gamma hemodynamic function in FEAT. Each condition was modeled as stimulus functions, contrasted with the baseline (rest) and all other conditions. Z (Gaussianised T/F) statistic images were thresholded at $p=0.05$ (uncorrected) (Smith et al. 2004; Woolrich et al. 2004). Registration of EPI images to high resolution T1 images and then subsequently to the Montreal Neurological Institute standard brain (MNI152) was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). A within-subject fixed effects analysis was then conducted to obtain the average BOLD response for each condition across the two experimental scans. Z (Gaussianised T/F) statistic images were again thresholded at $p=0.05$ (uncorrected).

The results of the fixed effects analysis was then entered into a higher-level repeated measures analysis using mixed (random) effects implemented in FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann, 2003; Woolrich, 2004). The design matrix included estimates for each condition and for all 24 participants (120 inputs in total). Given that previous studies have not specifically examined the proportion of control belonging to self versus other and to avoid potential biases of small volume correction, a conservative whole-brain analysis was carried out. Statistical images were thresholded using Gaussian random field theory with clusters determined by $Z > 3.78$ and a corrected cluster size significance threshold of $p = 0.05$ (Worsley, 2001). A group-level F-test statistical image, derived from contrasts representing linear combinations of the five conditions, was generated to identify brain regions displaying any significant differences between conditions. To identify regions positively and negatively related to performance on the task, participants' mean and SD of misattribution were also included as contrasts (centred around 0).

As the goal was to characterise the direction and shape of the differences between conditions (positive/negative/linear/quadratic), a series of anatomical masks were created. These were defined as active voxels ($Z > 3.78$ in the F-test statistical image) within hemisphere-specific regions determined by probabilistic structural atlases. Harvard-Oxford sub-cortical and cortical probabilistic atlases (FSLview 3.2.0, FSL software 5.0.4) were used for all brain regions apart from the cerebellum, which was defined by the MNI probabilistic structural atlas. Only voxels estimated at greater

than 50% probability of being in that brain structure were included in the mask. The number of voxels in each brain region was counted, and the voxel with the highest Z value located for each structure (Table 3.3). All masks were then transformed to participants' native space and percent signal change evoked by each of the 5 conditions was extracted from voxels within each mask (binarised) using FSL's Featquery tool (fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html).

To investigate the activation pattern in each region, a linear regression and a second-order polynomial were fitted to the responses at group level. A linear regression and a second-order polynomial were also fitted to each individual participant's responses and paired t-tests were used to test differences between the R-squared of the two fitted equations in each region. A multilevel regression (with conditions nested within individuals), which allowed intercepts to vary across participants, was also performed for each region to examine the effects of task performance on responses across conditions. Finally, we introduced mean-centered individual differences in task performance into the model (contrasts) as a predictor of BOLD response across all condition.

3.4. Results

3.4.1. Behavioural data

With data pooled over all participants and conditions the mean number of actions per block was 40.35 (SD=6.52), mean number of tones per block was 42.34 (SD=4.4), and mean attribution rating (scaled from 0 to 1) was 0.54 (SD=0.2).

To validate the probability-based manipulation, a measure of tap tone synchrony was calculated as the correlation between tap and tone after the onsets of the two variables were smoothed (butterworth low-pass filter: order=1, band=0.01). Mean correlation (r) between tap-tone synchrony and condition was -0.97 (± 0.01). Although there was a small tendency for participants to perform fewer taps as conditions increased (reduced control over tones), mean $r = -0.27$ (SD=0.17); this was shown to be non-significant for all but one participant (mean $p=0.34$, SD=0.26). The number of tones per block also did not vary significantly with condition, mean r

= 0.17 (SD=0.14) (mean $p=0.4$, SD=0.33). Table 3.1 shows tap-tone correlation, the number of taps and tones per block for each of the five conditions (with associated standard deviations). Taken together, this indicates that the manipulation aiming to systematically control the proportion of self-other control over tones had been successful and that conditions were well matched.

Table 3.1. Summary statistics by condition (C1 - C5) with data pooled over all participants.

	C1	C2	C3	C4	C5
Manipulation threshold	1	0.75	0.50	0.25	0
Tap tone correlation	1 (0.00)	0.72 (0.08)	0.52 (0.07)	0.28 (0.08)	0.02 (0.05)
Mean taps per block	42.80 (5.80)	40.78 (6.63)	40.15 (6.22)	39.06 (6.26)	38.93 (7.32)
Mean tones per block	42.80 (5.80)	43.43 (4.46)	44.65 (4.40)	43.16 (4.61)	39.07 (4.88)
Attribution	0.08 (0.13)	0.40 (0.23)	0.59 (0.24)	0.78 (0.19)	0.85 (0.17)
Misattribution	0.08 (0.13)	0.15 (0.23)	0.09 (0.24)	0.03 (0.19)	-0.15 (0.17)

Attribution ratings (provided on a 7-point scale) were analysed to check that the participants in the fMRI experiment rated the stimuli in line with what was intended. The attribution ratings of each participant were correlated with the five experimental conditions ranging from tones belonging to self to tones belonging to other. Given that all participants' correlation values were > 0.46 (mean $r = 0.77 \pm 0.12$) and significant (mean $p < 0.001$), all participants were included in the imaging analysis. It was further determined that attribution was not related to the number of taps per block ($r = -0.004$) nor to the number of tones per block ($r=0.05$). Quadratic and linear regressions predicting attribution responses by condition (1 to 5) were fitted for each individual and a paired sample t-test confirmed that the R-squared values for the quadratic polynomial ($M= 0.64$, SD=0.15) were significantly higher ($t(23)= -5.47$, $p < .0001$) than those derived from the linear regression ($M=0.6$, SD=0.17).

Misattribution, a measure of performance on the task, was calculated as the difference between attribution rating (scaled between 0 and 1) and condition

(rescaled from 0 to 1). Zero indicates a perfect score (i.e., no difference between perceived and actual control), with positive values indicating a bias towards other and negative values a bias towards self. Fig. 3.3 (a) shows the misattribution profile for all 24 participants with data pooled across conditions. Between-individual variation can be seen in at least two distinct ways: (1) how centered scores are around 0 (a perfect score) reflected in the standard deviation (SD) of misattribution; and (2) bias direction which can either point towards self (left-heavy distribution; negative score) or other (right-heavy distribution; positive score) reflected in mean (M) misattribution. Fig. 3.3 (b,c) shows how these two performance indicators – which we term error (SD misattribution) and bias (M misattribution) – varied across conditions, peaking near the middle of the self-to-other continuum (Table 3.2).

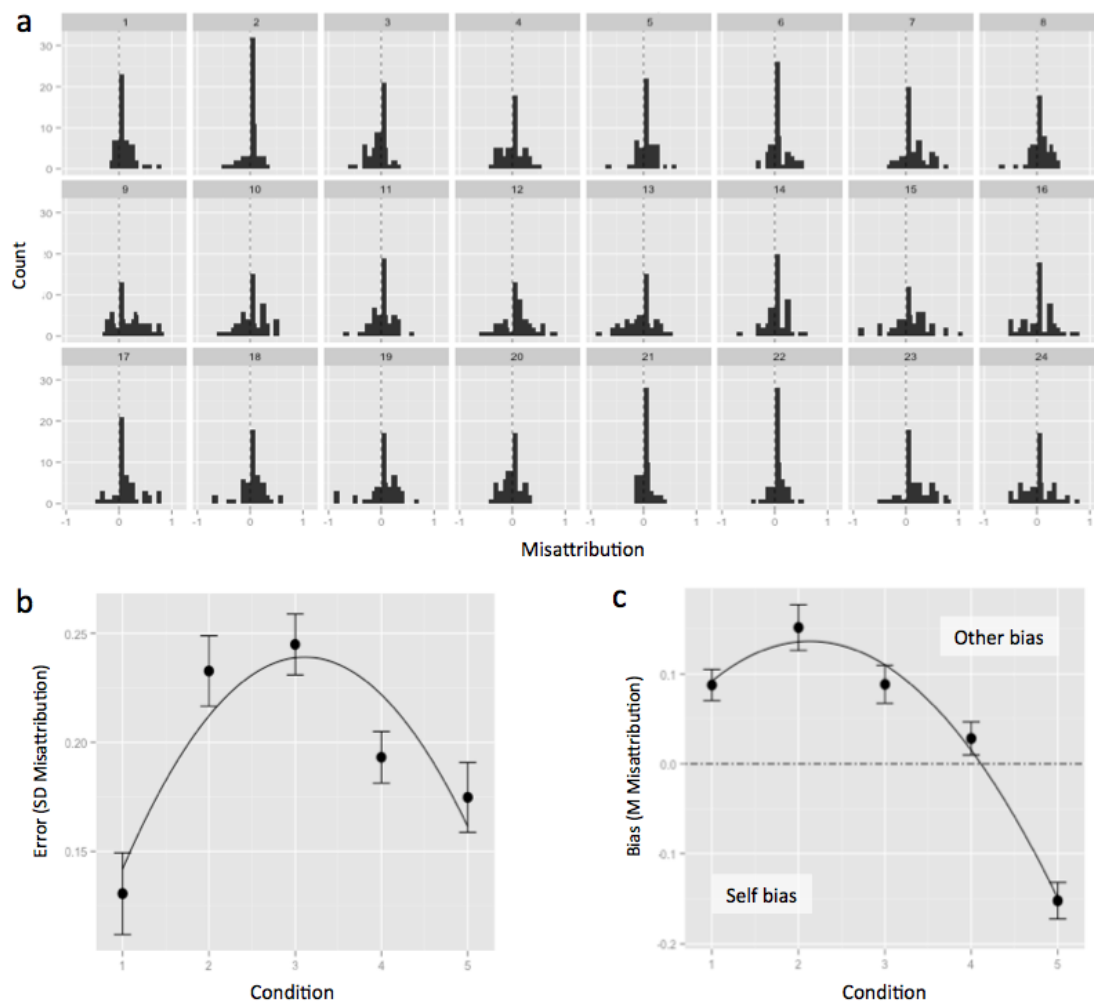


Fig. 3.3. (a) Histogram showing the misattribution profile for all 24 participants with data pooled across conditions. (b) Error (SD of misattribution) across conditions; (c) Bias (self/other) (M misattribution) across conditions. The line in (b) and (c) represents the quadratic polynomial that best fitted the data and bars represent standard errors of the mean.

Table 3.2. Multilevel regression (conditions nested within participants) predicting error and bias with the quadratic polynomial of condition (proportion of tones belonging to self versus other).

	Error	Bias
(Intercept)	0.03	-0.02
	(0.03)	(0.04)
Condition	0.14***	0.15***
	(0.02)	(0.03)
Condition^2	-0.02***	-0.03***
	(0.00)	(0.00)
AIC	-272.41	-213.40
BIC	-258.47	-199.47
Log Likelihood	141.21	111.70
Num. obs.	120	120
Num. groups: subject	24	24
Variance: subject.(Intercept)	0.00	0.00
Variance: Residual	0.00	0.01

*** p < 0.001, ** p < 0.01, * p < 0.05

Statistical models

3.4.2. Experimental scan

Fig. 3.4 shows the location of clusters within anatomically defined regions (thresholded at >50%) that showed significant differences between conditions in the whole-brain group analysis ($Z > 3.78$, cluster corrected at $p = 0.05$). The image results from an F-test and therefore represent all brain regions parametrically modulated by our task manipulation irrespective of response direction (positive, negative, quadratic) or participants' subjective ratings. Radiological convention is used, with the right hemisphere represented on the left side.

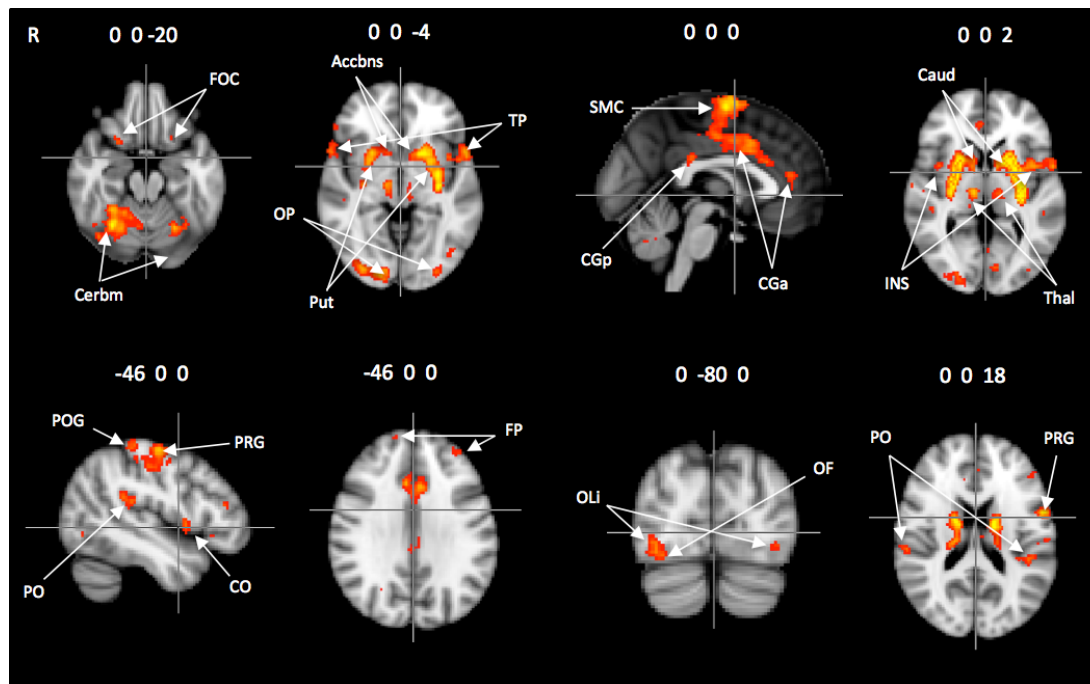


Fig. 3.4. Location of clusters that showed significant difference between conditions (F-test, $Z > 3.78$, cluster corrected at $p = 0.05$). Regions were defined by the Harvard-Oxford Cortical and Subcortical Structural Atlases and the MNI probabilistic structural atlas (Cerbm) and thresholded at $> 50\%$ probability. Images follow the radiological convention, with the right hemisphere represented on the left side. The Statistical image is overlaid on the MNI-152 2mm brain with MNI coordinates given for cross hair locations.

The name, abbreviation (Abbr), hemisphere (L/R), Brodmann area (BA), MNI coordinates and Z-statistic of peak voxels, and cluster size (mm^3) are provided for each of the 19 regions in Table 3.3. In brief, these included a number of cortical regions (Harvard-Oxford Cortical Structural Atlas) including, cingulate gyrus anterior division, cingulate gyrus posterior division, central opercular cortex, frontal orbital cortex, frontal pole, insular cortex, occipital pole, lateral occipital cortex inferior division, parietal operculum cortex, postcentral gyrus, precentral gyrus, supplementary motor cortex and temporal pole, as well as subcortical regions (Harvard-Oxford Subcortical Structural Atlas), including the accumbens, caudate, putamen, and thalamus. Areas of the cerebellum also showed significant response differences between conditions (MNI probabilistic structural atlas).

Table 3.3. MNI coordinates (x,y,z), peak voxels (Z) and size for clusters within anatomically defined regions (L= left; R=right) that showed significant difference between conditions (F-test, $Z>3.78$, cluster corrected at $p=0.05$). Regions are defined by the Harvard-Oxford Cortical and Subcortical Structural Atlases and the MNI probabilistic structural atlas (Cerbm) thresholded at $> 50\%$ probability. Region abbreviation (Abbr), hemisphere (L/R) and Brodmann areas (BA) associated with peak voxels are provided.

Region	Abbr	L/R	BA	MNI coordinates (x, y, z)			Z (max)	Size (cm3)
Accumbens	Accbns	R	25	10	12	-4	4.39	0.96
		L	25	-12	8	-8	5.51	1.84
Caudate	Caud	R	-	16	-4	20	5.51	9.12
		L	-	-14	-6	18	6.15	8.96
Cerebellum	Cerbms	R	-	32	58	-22	6.19	79.6
		L	19	-24	-60	-22	5.77	36.72
Cingulate Gyrus Anterior Division	CGa	R	24	6	24	26	6.11	34.4
		L	24	-4	12	34	5.69	29.76
Cingulate Gyrus Posterior Division	CGp	R	23	0	-32	26	4.61	3.12
		L	23	-4	-18	44	5.88	6.56
Central Opercular Cortex	CO	L	44	-38	4	8	5.61	4.8
Frontal Orbital Cortex	FOC	R	38	24	12	-22	4.61	4.8
		L	11	-24	32	-18	3.98	0.48
Frontal Pole	FP	R	9	16	58	30	4.01	0.72
		L	46	-36	46	30	4.23	1.76
Insular Cortex	INS	R	48	40	6	2	4.62	3.6
		L	48	-36	4	6	6.11	7.2
Occipital Fusiform Gyrus	OF	R	18	20	-84	-14	5.62	3.92
Lateral Occipital Cortex Inferior Division	OLi	R	19	40	-80	-12	4.39	1.2
		L	19	-40	-78	-8	4.69	2.64
Occipital Pole	OP	R	18	16	-92	-6	5.68	6.48
		L	18	-30	-94	-2	3.88	0.24
Parietal Operculum Cortex	PO	R	42	56	-26	18	4.07	0.16
		L	48	-48	-32	20	4.81	4.24
Postcentral Gyrus	POG	L	3	-48	-32	58	5.08	16.08
Precentral Gyrus	PRG	R	-	0	-16	52	3.83	0.8
		L	6	-56	6	16	5.97	28.96
Putamen	Put	R	48	30	-8	10	6.22	50.48
		L	48	-30	-20	4	6.97	58.96
Supplementary Motor Cortex	SMC	R	6	0	-6	64	6.08	9.92
		L	6	-4	-4	70	6.17	24.48
Thalamus	Thal	R	-	14	-18	12	6.16	31.12
		L	-	-12	-18	12	6.15	28.64
Temporal Pole	TP	R	-	58	10	-4	4.44	1.52
		L	-	-56	8	-4	5.03	1.84

The response pattern across conditions is shown for each region in Fig. 3.5. Responses showing similar patterns in the right and left hemispheres were combined. Response in all regions shown to be significant at group level displayed greater sensitivity to self, decreasing as the proportion of tones belonging to other increase. Another consistent observable feature is the quadratic character of the response in brain regions.

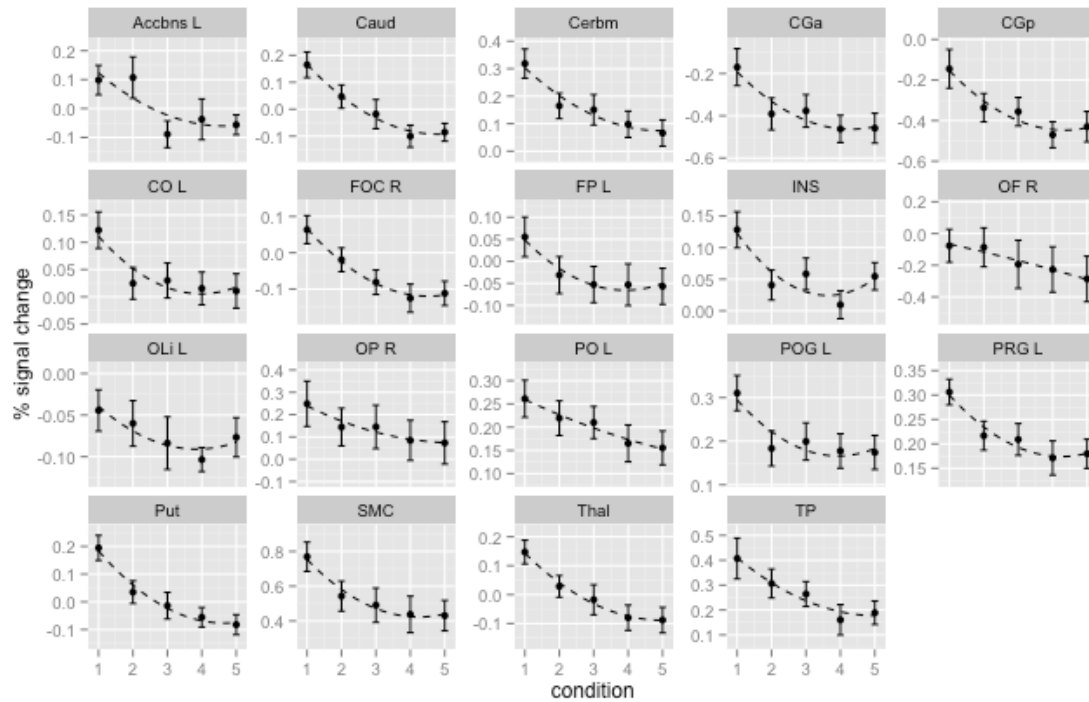


Fig. 3.5. Response patterns (% signal change) across conditions. Responses showing similar patterns in the right and left hemispheres were combined; L= left; R = right.

Results at group level showed bigger R-squared values for the quadratic polynomial than for the linear regression all brain regions. Quadratic and linear regressions were then fitted to the individual responses in each region and paired sample t-tests confirmed that the R-squared values for the quadratic polynomial were significantly higher than the R-squared for the linear regression in all the regions (Table 3.4). Although brain areas showing positive, negative, U-shaped and inverted U-shaped response patterns to our manipulation were observed at the individual level analysis, areas showing significant differences between conditions at the group level (mixed effects analysis), displayed a negative linear response with a positive quadratic component.

Table 3.4. R-squared values for the linear and quadratic polynomial regressions for each region with data pooled across participants (R=right; L=left; B= both). Results of paired t-tests comparing R-squared values for the linear and quadratic polynomial regressions fitted for each participant within each region (n is the number of participants included in the t-test; ML and SDL is the mean and standard deviation of R-squared for the linear regression, MQ and SDQ is the mean and standard deviation for the quadratic polynomial regression; df = n-1).

Regions		R-squared (group)		t-test (individual)						
		L	Q	n	ML	SDL	MQ	SDQ	t-value	95% CI
Accbns	L	0.61	0.69	19	0.41	0.25	0.66	0.26	-4.6***	0.14, 0.37
Caud	B	0.89	0.99	24	0.46	0.24	0.63	0.2	-4.61***	0.09, 0.25
Cerbm	B	0.86	0.94	24	0.53	0.28	0.66	0.26	-3.89**	0.06, 0.2
CGa	B	0.74	0.89	24	0.35	0.29	0.56	0.31	-4.36***	0.11, 0.32
CGp	B	0.79	0.94	24	0.4	0.32	0.66	0.31	-4.85***	0.15, 0.37
CO	L	0.63	0.86	24	0.38	0.27	0.62	0.28	-5.83***	0.15, 0.32
FOC	R	0.86	0.99	24	0.47	0.31	0.68	0.25	-3.81**	0.1, 0.33
FP	L	0.67	0.95	21	0.33	0.25	0.67	0.27	-5.72***	0.21, 0.46
INS	B	0.42	0.79	24	0.31	0.28	0.56	0.32	-6.07***	0.17, 0.34
OF	R	0.95	0.95	20	0.36	0.29	0.55	0.29	-4.44***	0.1, 0.28
OLi	L	0.57	0.85	6	0.12	0.12	0.44	0.24	-2.57*	0, 0.65
OP	R	0.87	0.93	24	0.47	0.3	0.67	0.3	-4.13***	0.1, 0.29
PO	L	0.95	0.96	24	0.43	0.31	0.57	0.31	-3.81**	0.06, 0.21
POG	L	0.58	0.82	24	0.31	0.25	0.56	0.26	-5.27***	0.15, 0.35
PRG	L	0.77	0.95	24	0.46	0.28	0.68	0.28	-4.8***	0.12, 0.31
Put	B	0.87	0.98	24	0.56	0.25	0.75	0.24	-4.69***	0.11, 0.28
SMC	B	0.79	0.97	24	0.39	0.29	0.65	0.27	-5.23***	0.16, 0.36
Thal	B	0.91	0.99	24	0.46	0.29	0.58	0.27	-4.03**	0.06, 0.17
TP	B	0.88	0.95	23	0.38	0.27	0.58	0.26	-4.58***	0.11, 0.29

*** p < 0.001, ** p < 0.01, * p < 0.05

Table 3.5 shows results of the multilevel regression for brain regions with significant main or interaction effects of error (SD misattribution) and/or significant main or interaction effects of bias (M misattribution). Using the R package visreg, version 2.0–4 (Breheny & Burchett, 2012), visualisation of the relationship between condition (x) error (upper row), and bias (lower row) in predicting percent signal change (blue to red) may be seen in Fig. 3.6. Low error predicted reduced response in the caudate, cingulate gyrus anterior division, precentral gyrus, putamen and right thalamus, particularly in the middle of the self-to-other continuum (a more pronounced quadratic u-shape). In the caudate, cerebellum, precentral gyrus, and putamen, a bias towards self was associated with a greater negative linear response while a bias towards other showed a positive linear trend. No bias in these regions

showed reduced activity in ambiguous conditions. Negative linear response was more pronounced in the cingulate gyrus anterior division and supplementary motor cortex as bias towards other increased.

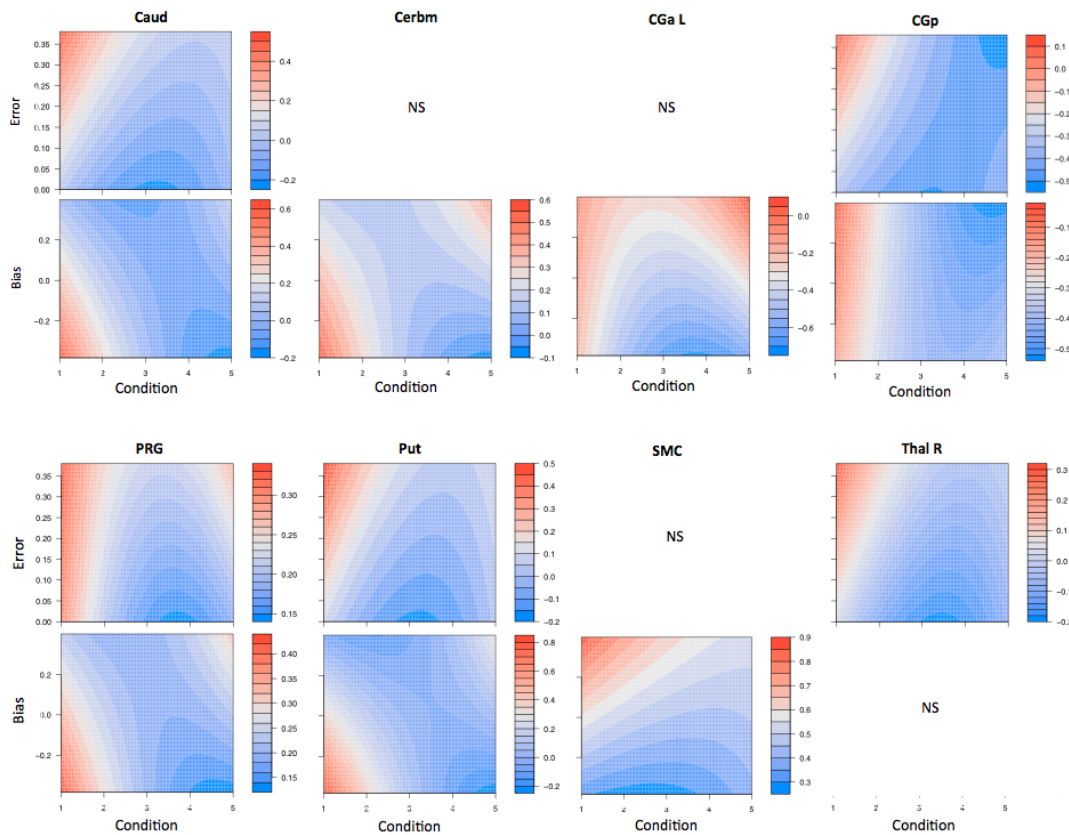


Fig. 3.6. Heat maps showing the relationship between condition (x) and error (SD misattribution) and/or bias (M misattribution) (y) in predicting responses (% signal change) (blue to red). Only regions with significant main and/or interaction effects are included in the figure. Responses showing similar patterns in the right and left hemispheres were combined.

Table 3.5. Multilevel regression (conditions nested within individuals) using condition, standard deviation (SD) and mean (M) of misattribution to predict responses within brain regions showing significant differences between conditions (F-test).

	Caud	Cerbm	CGa L	CGp	PRG	Put	SMC	Thal R
(Intercept)	-0.04 (0.04)	0.13** (0.05)	-0.40*** (0.07)	-0.41*** (0.06)	0.20*** (0.03)	-0.03 (0.04)	0.48*** (0.10)	-0.08 (0.04)
Condition	-0.09*** (0.02)	-0.06*** (0.02)	-0.06** (0.02)	-0.09*** (0.03)	-0.04*** (0.01)	-0.07*** (0.01)	-0.09*** (0.02)	-0.07*** (0.02)
Condition^2	0.03* (0.01)	0.03* (0.01)	0.05* (0.02)	0.06* (0.02)	0.02* (0.01)	0.04*** (0.01)	0.05* (0.02)	0.03* (0.01)
Error	0.54* (0.27)	0.44 (0.26)	0.64 (0.37)	0.79* (0.40)	0.25* (0.12)	0.47* (0.21)	0.55 (0.37)	0.52* (0.25)
Bias	-0.36* (0.27)	-0.24 (0.26)	-0.30 (0.37)	-0.48 (0.40)	-0.22* (0.12)	-0.27 (0.21)	-0.48 (0.37)	-0.26 (0.25)

	(0.18)	(0.17)	(0.24)	(0.26)	(0.09)	(0.14)	(0.24)	(0.17)
Condition : Error	-0.28*	-0.04	0.11	-0.29	-0.03	-0.11	-0.07	-0.11
	(0.13)	(0.13)	(0.18)	(0.21)	(0.06)	(0.10)	(0.18)	(0.13)
Condition : Bias	0.18	0.27*	0.37*	0.39*	0.14*	0.32**	0.36*	0.18
	(0.13)	(0.12)	(0.17)	(0.19)	(0.06)	(0.10)	(0.17)	(0.12)
AIC	-73.97	-71.12	18.94	40.28	-218.31	-119.09	31.96	-80.77
BIC	-34.94	-32.10	57.96	79.31	-179.29	-80.07	70.98	-41.74
Log Likelihood	50.98	49.56	4.53	-6.14	123.16	73.55	-1.98	54.38
Num. obs.	120	120	120	120	120	120	120	120
Num. groups: subject	24	24	24	24	24	24	24	24
Variance: subject.(Intercept)	0.04	0.05	0.09	0.07	0.02	0.03	0.22	0.03
Variance: Residual	0.01	0.01	0.03	0.03	0.00	0.01	0.02	0.01

*** p < 0.001, ** p < 0.01, * p < 0.05

Participants with greater overall error (Fig. 3.6, row 1) and bias (Fig. 3.6, row 2) towards other showed increased response during the task in medial prefrontal and posterior cingulate/precuneus areas (see red clusters in Fig. 3.7, row 1). A spatial cross correlation with intrinsic connectivity networks (ICN) as defined by Laird et al. (2013) showed greatest overlap with the default mode network (DMN) (ICN13) for both error ($r = .32$) and bias towards other ($r = .34$) – a network associated with internally focussed thought, theory of mind and social cognition tasks (Laird et al., 2013). In contrast, lower error most closely corresponded to a network involved in motor movements (ICN8: $r = .34$), and lower-level visual processing (ICN12: $r = .31$), while bias towards self showed greatest overlap with a network associated with auditory perception and discrimination (ICN16: $r = .28$).

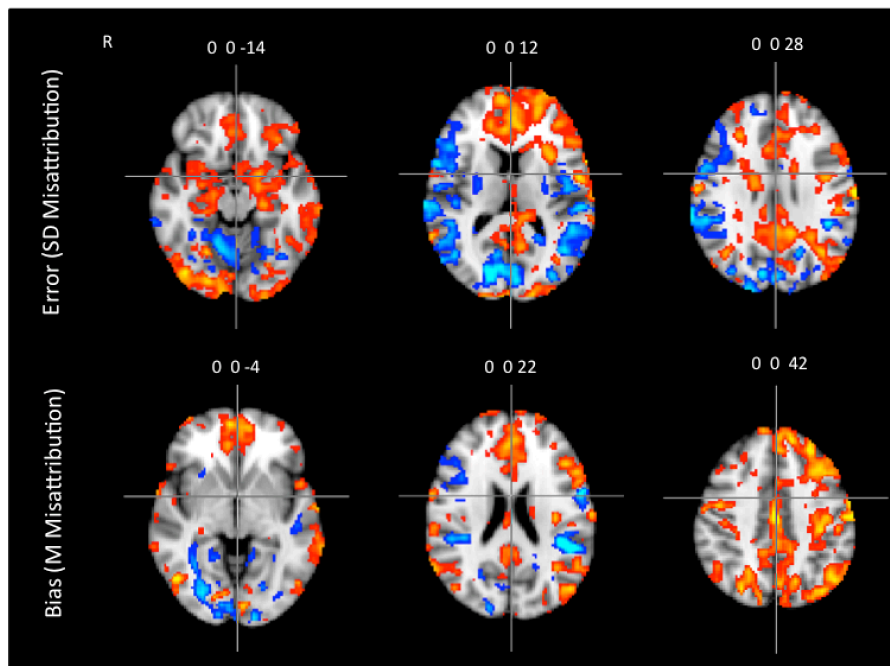


Fig. 3.7. Location of regions showing increased (red) and decreased (blue) responses in relation to overall error (SD Misattribution) and bias (M Misattribution). The Statistical image is thresholded at $Z > 3.78$ (cluster corrected at $p = 0.05$) overlaid on the MNI-152 2mm brain with MNI coordinates given for cross hair locations.

3.5. Discussion

In this study we investigated response patterns to modulating the probability that control over action-outcomes belonged to self or other. The aim was to shed light on how we process causal ambiguity – situations where information for differentiating between events caused by self or other/s is reduced. Participants performed a series of irregular finger taps whilst listening to a sequence of auditory tones that could either be produced by self or ‘other’ (randomised self-taps). Probability for self-other control was manipulated in 5 equal steps, resulting in a continuum ranging from all tones belonging to self (condition 1) to all tones belonged to other (condition 5). In contrast to a previous study that relied on subjective ratings (Fukushima), peak ambiguity in our paradigm could be objectively defined as the middle of this self-to-other continuum. Control in condition 3 was as likely to belong to self as to other, randomly fluctuating between the two over the 12 sec trial period. Following each trial, participants attributed control along a self-to-other continuum. Derived

performance measures were used to validate the task and shed additional light on the function of implicated regions.

Confirming findings of a previous behavioural study conducted by de Bezenac et al. (2015), results showed that this method was able to systematically vary tap-tone correlation over the 5 conditions ($r = -0.97$). Participants were also able to accurately attribute control to self and other (mean $r = 0.77$), indicating that the manipulation successfully captures cues used to explicitly evaluate causal relationships. The finding that task error (the deviation from a perfect score) and bias (direction of error) towards other peaked near the middle of the self-to-other continuum, supports the idea that allowing control over sensory outcomes to fluctuate between self and other over time reduces information for self-other differentiation (Fig. 3.3b). It also suggests a tendency to over estimate the amount of control that others possess in ambiguous contexts, though bias shifts towards self when other is in full control (Fig. 3.3c). As the task was neutral, a question for future research is how this pattern might be modulated by negatively and positively valenced stimuli.

To determine how the brain responded to the manipulation, regions showing significant differences between conditions were anatomically defined for each participant and percent signal change extracted for each condition. Linear and quadratic predictors were used to characterize stimulus-response functions. The main findings from this analysis were: (i) response in task-modulated regions was continuous; (ii) response in all regions decreased as the proportion of control belonging to other increased but also showed a positive quadratic component (overall U-shape pattern); and (iii) lower error and bias was associated with reduced response in ambiguous conditions in a number of regions.

Response in regions previously associated with self agency were also shown to be more sensitive to control belonging to self than to other in our manipulation, including the SMA (SMC), cerebellum, putamen, insula, ACC (CGa), and the DLPFC (FP) (Farrer & Frith, 2002; David et al., 2007; Haggard & Whitford, 2004; Lau et al., 2004; Farrer et al., 2003; Leube et al., 2003). Response in these regions varied continuously rather than categorically, consistent with the notion that agency

is often a question of degree in the brain, with relevant sensorimotor cues also varying in a continuous manner (Farrer et al., 2003; Gallagher, 2013).

Previous findings have also identified brain regions more sensitive to other than to self. One of the most consistent findings in neuroimaging research on the topic of agency is increased response during external control in inferior and posterior parietal areas (IPL; angular gyrus; temporo-parietal junction; PPC) (Sperduti et al., 2011; Moore et al., 2010; Farrer et al., 2003; McGuire et al., 1996; Spence et al., 1997; Ruby and Decety 2001; Farrer and Frith, 2002). However, this pattern was not observed in the present study. Here, no brain areas that showed significant response variation across conditions in the group analysis showed augmented activity when control belonged more to other. We suspect that this discrepancy reflects key differences in the design of studies. In distortion paradigms, sensorimotor mismatch is held constant within conditions (Farrer et al., 2003). In contrast, using our probability manipulation, the temporal distance between action and outcome (tone) is not controlled directly and varies randomly within conditions. This approach highlights agency-related regions sensitive to the overall proportion of self-other control over a given period of time (12 sec), rather than those involved in detecting local sensorimotor discrepancies. That previously observed inferior parietal areas were not identified through our manipulation may suggest greater correspondence with the latter function. Though these regions were found when comparing agency to non-agency (agency > colour) in Fukushima et al.'s study (2013), activity did not differentiate between judgements of self and non-self, suggesting a greater involvement at lower stages of the attribution process. In relation to the overall absence at the level of group of response relating to other, it may be that between-individual response variability increases in larger timescales as control belongs to other. Such an interpretation is supported by that fact that such stimulus-responses functions were observed at the individual level of analysis. Analyses of these patterns in relation to certain individual differences may be warranted.

The quadratic component found to be significant in all task-modulated regions suggests that areas involved in determining the proportion of control that self versus other possesses over sensory stimuli are also sensitive to the amount of information available for differentiating self from other. Identified regions included the ACC and

DLPFC – areas previously implicated in ambiguity processing during both decision-making (Huettel et al., 2005; Botvinick et al., 2001; Stern et al., 2010; Critchley et al., 2001) and agency (Fukushima et al., 2013). This suggests a role for these regions in processing ambiguity irrespective of domain (e.g., Neta et al., 2013). The pattern showing greatest response where attribution was most obvious, i.e. the extremes of the self-to-other continuum but particularly when self was in control, fits with the proposal that the DLPFC is involved in conflict resolution (Mansouri et al., 2009). The ambiguity implicit in most attribution tasks may partially explain the involvement of the DLPFC found in previous agency studies (Fink et al., 1999; Blakemore et al., 1998; Schnell et al., 2007; Farrer et al., 2008).

What is less clear is why the same response pattern was observed in the ACC (as opposed to an inverted U-shaped pattern), given its putative involvement in conflict detection (Carter et al., 2007). However, there is uncertainty about response direction to ambiguity in this region. Some imaging studies have found reliable ACC activation when tasks require the ongoing adjustment of cognitive resource allocation (Botvinick et al., 1999; Paus, 2001), with others showing relative deactivation during tasks also requiring cognitive control, for example, when performing antisaccades (Polli et al., 2005). Another factor that may contribute to determining response direction in the ACC is whether tasks require disambiguation (e.g., Neta et al., 2013). As, in the present study, participants responded along a self-to-other continuum following each trial, there was arguably less need to disambiguate than in other agency paradigms where categorical self/other responses were solicited.

Although decrease (relative deactivation) in BOLD signal is still poorly understood, it is thought to reflect neuronal inhibition (Frankenstein et al., 2003). There is evidence that inhibition plays a central role in executive functions including working memory (Rosen & Engle, 1998; Tomasi et al., 2006; Baddeley et al., 1998). It has also been linked to accurate performance in cognitive control tasks (Polli et al., 2005) and complex skills, such as the suppression of possibilities related to a target concept in semantic processing (Faust & Gernsbacher, 1996; Mirman & Graziano, 2013). Deficits in inhibitory function have been associated with psychopathologies, including schizophrenia and epilepsy (Clark, 1996). Consistent with these studies, reduced response in ambiguous conditions also correlated with low error and bias.

This may reflect a strategy of selectively suppressing internal or external stimuli in ambiguous conditions, such that definitive attribution judgments are suspended during the information-gathering period. Inhibition, defined as the ability to suppress dominant, automatic, or prepotent responses (Stroop, 1935), among other aspects of cognitive control, may play a key role in the neural architecture for responding to causal ambiguity as it occurs over time.

Individuals who demonstrated stronger bias towards other throughout the task showed more activity in MPFC, precuneus, PCC and the ACC – areas that include key nodes of the DMN. Neuroimaging studies have also shown task-related deactivations in DMN regions accentuated by performance accuracy and task difficulty (Harrison et al., 2011; Gilbert et al., 2012; Polli et al., 2005). It has been suggested that this represents the reallocation of processing resources (McKiernan et al., 2003). It may be that individuals who make more attribution errors have a less developed ability to allocate or distribute resources to lower-level perceptual areas associated with low error and bias in our study. Broca's region (BA 44, 45), a motor speech-production area involved in understanding, imitating and sequencing action (Nishitani et al., 2004), was also found to be sensitive to individual differences in task performance. Participants who made more errors had greater response in left hemisphere areas, primarily associated with language-related functions (Bookheimer, 2002), while less error and bias predicted greater response in the right hemisphere, implicated in the voluntary inhibition of imitative (Brass et al., 2005), perceptual sequencing tasks (Schubotz & von Cramon, 2004), and in viewing ambiguous facial expressions (Nakamura et al., 1999).

A number of subcortical regions less featured in previous agency studies were shown to be sensitive to our probability manipulation, including the putamen, caudate, nucleus accumbens, and thalamus. These regions, connected to widely distributed areas of the cortex and the PFC in particular (Choi et al., 2012), are involved in the regulation of dopamine, which is fundamental to a diverse range of cognitive and attentional processes including attention-mediated allocation of cognitive resources (see review by Nieoullon, 2002), many of which are relevant to agency. These include motivation associated with motor control and seeking behaviour, the planning of voluntary action, the on-line monitoring of its environmental context,

temporal estimation, and anticipatory adaptive learning involving executive functions and working memory (Arias-Carrión & Pöppel, 2007; Groenewegen, 2003; Nieoullon, 2002). These functions are likely to be implicated in monitoring causal relationships particularly as they occur over time during action performance. Altered dopamine neurotransmission has also been implicated in a number of disorders involving distortions in time perception and timed performance (Allman & Meck, 2012), including schizophrenia, Parkinson's disease, ADHD and autism (Swerdlow & Koob, 1987; Cohen & Servan-Schreiber, 1993; Bernheimer et al., 1973; Berger and Posner, 2000; Goldberg et al., 1987). That brain regions involved in time-perception were identified in the present study makes sense given that self-other difference was defined temporally in our task.

The subcortical regions identified in this study have also been shown to be responsive to varied and even contradictory stimulus types, including reward, aversion, and unpredictability (Volman et al., 2013), leading to their proposed involvement in situated salience (Luna et al., 2004; Berridge & Robinson, 1998; Schultz et al. 1997). Other regions found in our study, the ACC and insula in particular, are also core nodes of the salience network – a system thought to contribute to affective and social cognition by enabling the selection of the most relevant internal and external stimuli (Seeley et al., 2007; Menon & Uddin, 2010). In a previous parametric fMRI study, a U-shaped response found in the amygdala in relation to face trustworthiness was interpreted as reflecting the region's role in processing behaviourally salient events as opposed to fear that would predict a positive linear response (Said et al., 2009). However, a later study found that same pattern in response to face trustworthiness and gender, not only in the amygdala, but also in all other face-selective regions investigated (Mattavelli et al., 2012). This finding taken with those of the current study suggests that this type of U-shaped salience response may be wide spread in the brain, with stimuli processed in terms of their distinction from an ambiguous average. In a neutral task at least, situations that clearly point to self or other may inform subsequent behaviour more directly than those that are causally ambiguous.

Despite the significantly better fit afforded by including a quadratic polynomial to the model, response was greater when control belonged to self than to other. This

may be explained by the relative similarity between self- and other-generated tones that only varied in their temporal relationship to the participant's taps. In everyday experience stimuli belonging to other is generally more starkly defined. It is possible that more pronounced difference between stimuli generated by self and those generated by other would result in an actual U-shape. This could be examined in future research by manipulating a greater number of naturally occurring cues that contribute to self-other differentiation, including for example auditory differences in location, timbre and intensity, or cues from multiple sensory modalities. Interestingly, the region found to have the most pronounced quadratic component in the present study was the insula, which may explain why the initial finding associating insula activity with sense of self control was not systematically replicated (David et al., 2008).

Another avenue for further investigation into the role of ambiguity in agency processing is to compare neural response to ambiguity in self-other differentiation with ambiguity as it occurs in 'other-other' differentiation (i.e., a passive self distinguishing one person from another). Given the absence of internally-derived sensorimotor information in the case of the latter (e.g., proprioception), ambiguity is likely to be even more prominent, though arguably less salient/relevant to self. Hallucinations have been associated with a reduced ability to use such internal signals to make accurate predictions about the effects self-produced thoughts and actions (Frith, 2005), therefore, identifying neural correlates specifically associated with ambiguity in self-other differentiation through direct contrast with other-other differentiation may eventually also contribute to clinical understanding.

3.6. Conclusions

In summary, our results provide evidence suggesting that causal ambiguity is a prominent feature in self-other attribution and the experience of agency, more generally. We used a novel approach that allowed ambiguity, as it occurs over time, to be objectively defined and parametrically manipulated. Brain regions previously identified in agency, motor cognition, salience, and ambiguity processing showed greatest sensitivity to self-control and an attenuated response in conditions where

information for self-other differentiation was reduced. This response pattern was associated with task performance in a number of task-related regions, with low error and bias predicting reduced response. Individuals who made more errors and biased responses over the entire task also showed increased activity in regions associated with the DMN. Overall these findings suggest that causal relationships are processed in terms of their distinctiveness from uncertain contexts. A greater understanding of ambiguity-processing in agency may shed additional light on positive symptoms associated with psychosis. Future studies, for example, could explore how response across a self-to-other continuum is modulated by individual differences associated with agency deficits in both neutral and valenced contexts and compare neural response to ambiguity in self-other and other-other differentiation.

3.7. Acknowledgements

The authors would like to acknowledge the Institute of Psychology Health and Society, University of Liverpool for funding data collection and a studentship. We thank Rachel Swindells and Noreen O’Sullivan for their helpful discussions and Oran Quinn for his assistance with data collection.

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CHAPTER 4

Exploring individual differences in self-other attribution with fMRI

[de Bézenac, C., Sluming, V., Corcoran, R. (under review). Exploring individual differences in self-other attribution with fMRI. *Consciousness and Cognition*]

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4.1. Abstract

The ability to distinguish the effects of own from others' actions is a prerequisite for effective interpersonal functioning. Difficulties in self-other differentiation have been linked to positive symptoms of schizophrenia such as hallucinations, with causally ambiguous situations where actions of both self and other produce similar results proving a universal challenge. Evidence has shown that individuals who spend time in ambiguous contexts, such as music-making, may become better at self-other discrimination. This study explores brain-behaviour relationships associated with self-other processing, in differentially ambiguous contexts. Using a block-design fMRI paradigm, we manipulated the probability that a participant's finger taps would result in auditory tones as opposed to tones generated by 'another's finger taps' with ambiguity at its highest when the probability of self- and other-produced tones was equal. Positive schizotypy and the inability to tolerate ambiguity predicted increased activation in multiple brain networks (i.e., DMN, visual, auditory and sensorimotor) and regions (i.e., cingulate and temporal) while processing ambiguous stimuli. In contrast, reduced response in the same areas was associated with

increasing musical experience and improving task performance. Our findings suggest the possibility that practice-induced improvement in self-other differentiation under conditions of maximal uncertainty may prove an alternative treatment for troubling hallucinations.

Keywords: fMRI; Agency; causal ambiguity; self-other processing; schizotypy; healthy brain; functional networks; musical experience; ambiguity-processing

Highlights

- Individual differences predicted response in causally ambiguous conditions
- Overall response to ambiguity increased with positive schizotypy
- Ambiguity-related response decreased with task performance and musical experience

4.2. Introduction

4.2.1. Self-other differentiation

The ability to accurately distinguish acts of the ‘self’ from those of ‘others’ is a prerequisite for meaningful social interaction. Both internally and externally derived information is typically present to help self-other differentiation. For example, outcomes belonging to self tend to closely match preceding intentions and actions (Wolpert et al. 1995; Frith, 2005; Wegner, 2003). Agency – the sense of being the cause – is therefore thought to be a multifaceted phenomenon, involving somatosensory signals, body schema, and also higher-order intentions and goals (Gallagher, 2000; Synofzik, Vosgerau & Newen, 2008).

A growing body of research has examined the neural correlates of agency, by comparing response to the unaltered visual feedback of a participant’s action with feedback that has been distorted using delay (Leube et al. 2003) or spatial

displacement (Farrer et al. 2003; David et al. 2007). These studies have implicated several distributed brain regions, with action attribution to self and other supported by partially distinct neural substrates (for reviews see Sperduti et al., 2011, David et al., 2008). For example, activation in the putamen, insula, cerebellum, and parieto-occipital sulcus has been linked to self-agency (congruent vs. distorted feedback), though findings vary across studies (Farrer & Frith, 2002; David et al., 2007; Haggard & Whitford, 2004; Lau et al., 2004; Farrer et al., 2003; Leube et al., 2003). There is more consistent evidence that the right inferior parietal lobe (IPL), the supplementary motor area (SMA), pre-SMA, precuneus, and medial prefrontal cortex are sensitive to the processing of distorted (assumed not-self) stimuli (Moore et al., 2010; Farrer et al., 2003; McGuire, Silbersweig, & Frith, 1996; Spence et al., 1997; Ruby and Decety, 2001; Farrer & Frith, 2002; Pfeifer, Lieberman, & Dapretto, 2007).

4.2.2. Challenges in self-other differentiation

Differentiating self from other is complex, not always straightforward. Mental states, intentions, biases, beliefs, and expectations influence how an individual attributes action outcomes to self and other (Dijksterhuis et al., 2008; Farrer et al., 2008; Sato, 2009; Synofzik, Thier, & Lindner, 2006; Wegner, 2003). Moreover, difficulties distinguishing between self-produced versus externally-caused thoughts and actions is thought to constitute one of the core cognitive features of schizophrenia reflected in positive symptoms like delusions of control and auditory verbal hallucinations and reflected in positive schizotypy (Ditman & Kuperberg, 2005; Frith, 2005; Jeannerod, 2009; Spence et al., 1997; Woodruff, 2004; Lindner et al., 2005; Parnas & Handest, 2003; Johns et al., 2001; Hauser et al., 2011; de Bezenac et al., 2015; Sugimori, Asai, and Tanno, 2011). Furthermore, neuroimaging has identified increased temporal and inferior parietal activation associated with perceived externally generated action in patients with positive symptoms (Spence et al., 1997; Jardri et al., 2011; Farrer et al., 2004). Hallucinations have been associated with neural dysfunction in multiple cortical and subcortical regions, including over-activation in cingulate and auditory temporal areas (reviewed by Allen et al. 2008) with several functional networks more recently implicated. Examples include reduced task-related suppression of the default mode network (DMN) (Williamson and Allman, 2012) and abnormalities in

language-related, temporal, subcortical and salience networks (Welsh et al., 2010; Wolf et al., 2011; Liemburg et al., 2012; White et al., 2010).

While the focus of much of the clinically-oriented agency literature has been on mechanisms internal to the perceiver (see review by Moore & Fletcher, 2012), misattribution can also be driven by external, situational factors (Wegner, 2002; 2003). Notably, social contexts are often characterised by challenges in attributing intentions, actions, and their outcomes to ourselves and other agents (Frith, 2007). This is because events in such contexts tend to be co-produced, neither fully belonging to self or to other but resulting from the mutually regulated actions of both (Badino et al., 2014; Wing et al., 2014; Sebanz, Bekkering, & Knoblich, 2006; Konvalinka et al., 2010). Take for instance the experience of singing in a choir and not knowing which part of the overall sound belongs to self as opposed to other choir members performing similar or complementary actions. The more integrated or similar self-produced outcomes are to those belonging to other(s) (e.g., in time, location, form and intensity), the less information there is on which to base self-other differentiation. In these contexts we may experience stimuli generated by self as belonging to other (other bias), or claim ownership of the results of others' actions (self bias).

Still, little is known about the role that lack of discriminating information (i.e., ambiguity) plays in self-other processing and how the brain responds to situations with reduced information to guide differentiation (Gallagher, 2013). This may be partly due to methodological challenges associated with adequately addressing this research question. Fukushima et al., (2013) used the feedback distortion approach, adjusting delay between action and visual feedback to make agency maximally ambiguous for each individual. They found that ambiguity in attribution was related to activity in temporo-parietal regions (IPL, TPJ), medial frontal areas (SMA, ACC), the DLPFC, and frontal operculum/insula regions, though the set-up employed did not allow ambiguity-related response to be compared to response related to non-ambiguous conditions. In a recent behavioural study, we developed a tapping task that systematically manipulated the probability that self- or other-produced taps would result in auditory tones (de Bezenac et al., 2015), with the 'other' made up of the randomised tap timings of self. In contrast to previously used feedback distortion

paradigms, this approach allowed control over stimuli to be systematically manipulated along a self-to-other continuum meaning that causal ambiguity could be objectivity defined as the middle of the continuum where likelihood of tones belonging to self and other was equal. Findings from a subsequent fMRI study (de Bezenac, Sluming & Corcoran, under review) showed decreased response in the middle of the self-to-other continuum in a network of cortical and subcortical regions associated with self-agency. However, increased ambiguity-related response was not clear within the group results. The authors speculated that this was likely due to individual differences in factors associated with this self-other discrimination ability, suggesting the need for a nuanced analysis taking into account the most likely relevant variables

4.2.3. Refining differentiation abilities

The experience of ‘not knowing who has done what’ promoted by behavioural synchrony can be highly enjoyable and an intrinsically motivating aspect of joint activities such as music, dance, sport, and even everyday conversation (Coey et al., 2012; Richardson et al., 2007; Himberg et al., 2015). However, such activities also explicitly require participants to monitor contributions of self in relation to those of others: failure to do so can result in unintentional, less effective and non-adaptive outcomes. It is possible that enjoyable but challenging joint-activities that require self-other differentiation may provide optimal conditions for refining this skill. This could explain some of the significant functional changes in motor, auditory and speech processing regions previously shown to be associated with musical training (reviewed in François et al., 2015). For example, Chen et al. (2012) observed practice-induced activation reductions in motor-related areas, which may reflect developed functional efficiency (Jäncke et al., 2000). This idea allows certain predictions to be made: individuals who spend more time engaged in such ambiguous contexts should be better than average at distinguishing self- from other-acts. Such a finding would have clinical implications, suggesting that the ability to accurately differentiate self and other, widely agreed to be causally related to positive symptoms of schizophrenia, is malleable and honed through practice.

De Bezenac et al. (2015) explored this idea using the probability manipulation described above. Results showed that variance between individuals increased in

ambiguous conditions. Furthermore it was in these conditions that misattribution towards other decreased with years of music-making experience and increased with hallucination proneness.

4.2.4. Ambiguity-processing

Outside of agency-focussed research, ambiguity has been studied as a key dimension of everyday experience that significantly influences behaviour and decision-making (Yoshida & Ishii, 2006). Imaging research has implicated the anterior cingulate cortex (ACC) (Botvinick et al., 2001; Stern et al., 2010; Critchley et al., 2001; Krain et al., 2006), an area thought to be involved in conflict detection (Carter et al., 2007), the DLPFC (Huettel et al., 2005), a region associated with conflict resolution and context processing (Mansouri et al., 2009), the IPL (Britz et al., 2009; Volz et al., 2003), as well as the amygdala (Hsu et al., 2005; Zaretsky et al., 2010). The latter may be related to the anxiety that can be induced by uncertainties in the environment. The inability to tolerate ambiguity (treating situations lacking information as threatening rather than promising) – a concept linked to cognitive flexibility and typically measured by a self-report questionnaire (Budner, 1962; Furnham and Ribchester, 1995) – has been implicated in a range of psychopathological disorders including general anxiety disorder (Buhr & Dugas, 2002; Dugas, Gosselin, & Ladouceur, 2001), obsessive-compulsive disorder (Tolin, Woods, & Abramowitz, 2003), and psychosis-proneness (Broome et al., 2007; Colbert & Peters, 2002). It has also been related to prejudicial attitudes (Frenkel-Brunswik, 1949), and inversely correlated to mindfulness (Sauer et al., 2012), and critical thinking (Facione, Facione, & Sanchez, 1994). Ambiguous stimuli (bistable perception) have also been used to examine ambiguity-processing. Individual variation in patterns of spontaneous perceptual switching between two or more available percepts has been related to a number of factors, including working memory (Allen et al., 2011), mindfulness (Sauer et al., 2012), mood state (Hupé & Rubin, 2003), and genetic traits related to dopamine and serotonin systems (Miller et al. 2010; Shannon et al. 2011; Kondo et al., 2011). Though findings have not been consistent (Keil et al., 1998), a reduced number of perceptual switches and the inability to control which percept is attended to has been linked to clinical conditions including schizophrenia and bipolar disorder (McBain et al., 2011; Miller et al., 2003).

4.2.5. Experimental approach

The aim of this exploratory fMRI study is to shed light on self-other processing in the brain by investigating the relationship between contextual factors relating to the locus of control and individual traits likely to be implicated in this process. Following previous work in our lab (de Bezenac et al., 2015; de Bezenac et al., 2016), a cohort of healthy volunteers completed a tapping task in the scanner which parametrically manipulated the probability that actions of self or ‘other’ would result in auditory tones in 5 conditions ranging from tone control belonging fully to self to belonging fully to other. Ambiguity peaked where the probability for self and other control was equal in the middle of the continuum. We examined task-related neural response using individual-difference variables as predictors. Given its phenomenological and behavioural overlap with clinical symptoms of schizophrenia (Ettinger et al., 2015), we used a multi-dimensional measure of schizotypy (shortened O-LIFE: Mason, Linney, & Claridge, 2005). Other predictors used in the analysis included task performance, music-making experience (based on the hypothesis that this is related to efficient self-other processing), and indicators of ambiguity processing style, namely the tolerance of ambiguity scale (Budner, 1962) and an auditory stream task (Kondo et al., 2011). There is an increasing number of neuroimaging studies treating response variability between individuals as meaningfully associated with cognitive and behavioural factors that constrain real world function, rather than as noise (Bassett et al., 2009, van den Heuvel et al., 2009). Delineating these brain-behaviour relationships during a self-other attribution task, we believe, can shed light on the processes involved in self-other differentiation and help to formulate testable hypotheses concerning the aetiology of agency-related symptoms of schizophrenia.

Two different approaches were taken to the analysis of the imaging data. We first conducted a standard whole-brain univariate analysis examining response in brain regions associated with control belonging to self (negative linear response in relation to conditions 1-5), other (positive linear response) and ambiguity between self and other (positive/negative quadratic response) and how response was predicted by individual differences. We then examined how network time-courses, derived from a group Independent Component Analysis (ICA), were modulated by the task and their functional connectivity with the rest of the brain (dual regression), in relation to

individual differences. In recent years there has been a shift in the neuroimaging literature towards considering networks as opposed to isolated regions as the unit of analysis in elucidating neural processes (Friston, 2011; Meehan & Bressler, 2012). A data-driven ICA approach has a number of advantages over more conventional univariate and seed-based correlation techniques, including the identification of response patterns in partially overlapping regions and reducing sensitivity to artifacts (Laird et al., 2011; Smith et al., 2009; Bressler and Menon, 2010). Network-based methods have also been effective in highlighting neural differences between schizophrenia patients and matched controls (reviewed in Williamson and Allman, 2012). Despite this, few studies have examined agency using network-based approaches (David, Newen & Vogeley, 2008). It is also not yet clear whether the spatially distributed regions implicated in agency function together, covarying as one or more intrinsic networks. We report the results of both analytic approaches here to allow findings to be considered in relation to patterns of activations reported in previous research on agency, whilst providing a novel network-level account of agency-related brain function that can be considered alongside network-based clinical evidence.

Detailed hypotheses were not advanced due to the exploratory nature of the study. However, based on previous evidence showing between-participant variation in misattribution to increase with ambiguity (de Bezenac et al., 2015), we broadly hypothesised that individual differences would predict response to ambiguous conditions. Given previous over-activation findings associated with hallucinations, we expected positive schizotypy and an inability to tolerate ambiguity to correlate with increased network recruitment, as well as in regions previously associated with both agency and ambiguity-processing. Conversely, task performance, musical experience and the bistable auditory stream task were expected to reflect more efficient self-other processing and, thus, to predict neural response in the opposite direction.

4.3. Methods

4.3.1. Participants

Twenty-four healthy right-handed student volunteers (12 male, 12 female) took part in this study (age: $M = 32.3$, $SD = 8.4$). Participants reported normal hearing, vision, and somatosensory perception and no known history of mental illness or neurological abnormalities. The study was approved by the ethics committee of the University of Liverpool and conducted in accordance with its policies.

4.3.2. Experimental stimuli

Stimulus presentation and participant response collection were managed using Pure Data (Puckette, 1996: <http://puredata.info/>). In the scanner, the experimental task was completed using an MRI-compatible response box. Instructions were provided visually via a projector screen seen through inverting mirrors. Auditory stimuli were presented diotically through pneumatic tubes within the ear protector at a volume of 95 dB and consisted of a tone (cosine wave, 262 Hz; 100 ms duration; 20 ms onset ramp; 5 ms offset ramp). This tone was triggered by one of the three response box buttons positioned on the participant's right thigh. In a pre-scan test, all participants reported that the tone could be clearly heard without perceptible delay during data acquisition (inherent system delay = 25ms).

During the task, tones could either result from the participant's own actions (self) or from the actions of another individual (other). To ensure consistency across conditions, taps produced by 'other' consisted of the participant's own 50 previous inter-tap intervals played back in a random order. The probability that a tap belonging to self or other would result in a tone was manipulated in five equal steps, corresponding to the five experimental conditions. Probability manipulation was achieved by generating a random number between 0 and 1 every time a self or other tap occurred. Each of the 5 conditions (C1-5) was associated with a threshold below which tones generated by self would be heard and above which tones generated by other would be heard: $C1 = 1$; $C2 = .75$; $C3 = .5$; $C4 = .25$; $C5 = 0$. These thresholds meant that in C1 all tones were self-generated (maximal tap-tone synchrony), while in C5 all tones were generated by other (maximal tap-tone asynchrony). In C3 (the middle of the self to other continuum) tone control was equally distributed, shifting

between self and other (semi-synchrony). Fig. 5.1 provides an example of the result of our manipulation where temporal relationships between tone onsets, self- and other-taps are depicted.

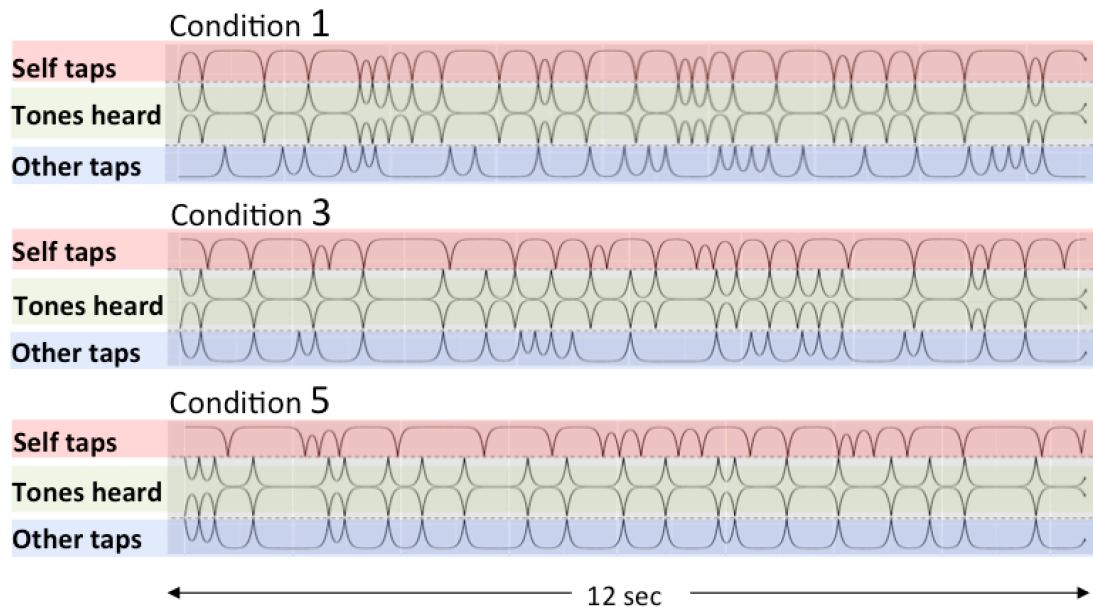


Fig. 4.1. Temporal relationships between self-produced taps (red), tone heard (green), and taps of other (blue). Data shown are from one arbitrarily chosen participant from a pilot study in conditions equivalent to 1 (self fully in control), 3 (ambiguous control: the probability that self or other will produce a tone is equal), and 5 (other fully in control). Peaks in top lines (which represent the participant's irregular taps), are synchronised with tones heard in condition 1 (peaks meet), semi-synchronised in condition 3, and asynchronised in condition 5.

4.3.3. Imaging parameters

Scanning was performed at the Magnetic Resonance And Image Analysis Research Centre (MARIARC), University of Liverpool with a Siemens Trio 3.0 Tesla (Siemens, Erlangen, Germany), whole body MRI system, equipped with an eight-channel phased array head coil. Foam padding and head restraints were used to minimise head movement during data-acquisition. For fMRI scanning, echo-planar images were acquired using a T2* weighted gradient echo sequence with blood oxygen level dependent (BOLD) contrast (TR = 3000 ms; TE = 30 ms; flip angle = 90°, 49 slices, distance factor = 10 mm, interleaved multi-slice mode, matrix = 64 x 64; FOV = 192 mm; acquisition voxel size = 2.7 mm³). Each experimental scan consisted of 197 contiguous EPI functional whole head volumes. The first eight volumes of each run were automatically removed to allow for magnetic stabilization. T1-weighted MR images were acquired sagittally for each participant with the

following parameters: TE 5.57ms, TR 2040 ms, flip angle 8°, FOV=256×256 mm², 176 slices, voxel size 1 mm³.

4.3.4. Experimental scan

Participants were asked to perform series of irregular taps (“like Morse code”) using their right index finger whilst listening to a sequence of tones. A recorded example of tapping was provided and a practice session outside the scanner ensured that tap density was similar across participants and conditions. Participants were told that tones could either result from their own actions (self) or from the actions of another individual (referred to as ‘other’), and that the proportion tones belonging to self or other would vary between trials. Experimental blocks consisted of 12 seconds of tapping, indicated on the screen by the word “Play”. After each block, participants were given 5 seconds to report the proportion of control that they felt belonged to self or other along a continuum represented by a rectangular box within which a vertical bar appeared in a randomised initial position. Using the two remaining keys of the response box, participants were able to move that bar towards self (left) or other (right) to represent the locus of experienced control. The rating period was followed by a 6 second fixation cross (jittered by up to 2 seconds) to ensure that BOLD response returned to baseline levels, including a 3 digit countdown to the start of the following block (500 ms per digit). Each of the 5 conditions was repeated 10 times and presented to participants in a pseudo-random order, with the constraint that consecutive conditions were not presented in consecutive blocks. The 50 blocks were divided into two 12-minute scans (25 blocks in each). A schematic representation of the experimental paradigm is provided in Fig. 4.2. Participants also underwent a T1/T2 structural, resting-state and DTI scan, meaning that scanning sessions were approximately 50 minutes long.

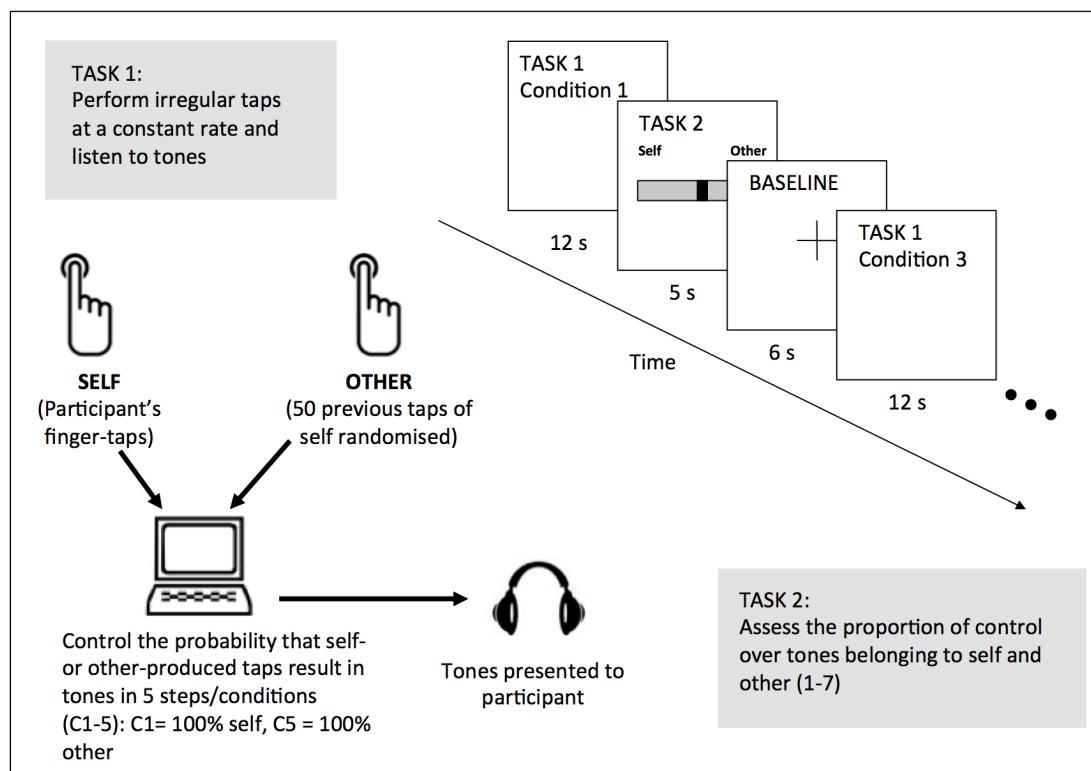


Fig. 4.2. Schematic representation of the experimental paradigm.

4.3.5. Behavioural and self-report measures

Following the scanning session, participants completed behavioural tasks (programmed in Pure Data) and electronic versions of self-report questionnaires in a quiet room using a MacMini computer.

The experimental task was completed outside the scanner. The probability manipulation was identical to the scanner task, although there were 10, instead of 5, conditions from self to other. In this version of the task, previously described in detail in de Bezenac et al. (2015), participants used a mouse to indicate the proportion of control belonging to self and other along a continuum and responses were not speeded. These differences allowed greater precision in the assessment of agency performance (Perf) without scanner-related constraints and distractions. Perf was calculated as the correlation between participants' attribution ratings (subjective locus of control) ranging from self to other and tap-tone asynchrony (objective locus of control). The latter was computed as the correlation between Butterworth filtered time-series of tap and tone onsets (see waves in Fig. 4.1). A high correlation thus

indicated the locus of control subjectively experienced by the participant matched the actual control that they had in relation to other. The task lasted approximately 15 minutes.

During the auditory streaming (AS) task, stimuli were presented at 65 dB diotically through headphones (PX-660, Pro-Luxe). In accordance with the standard protocol describe by Kondo et al (2011), stimuli consisted of 225 repetitions of a triplet tone that comprised high (H) and low (L) tones with silent intervals. The duration of each tone was 40 ms, which included rising and falling cosine ramps of 10 ms. The stimulus onset asynchrony between the L tones was 200 ms, whereas that between the H tones was 400 ms. The interval between H and L tones was 6 semitones: H = 1213 Hz and L = 823 Hz. Participants were instructed to close their eyes and listen to the sound sequence passively. They were told to press a key with their dominant hand every time a perceptual shift occurred. Shifts could occur between hearing the stimuli as a single coherent stream (with a galloping rhythm) or as one of two segregated streams (with isochronous rhythms in the high and the low). The stimuli were presented to participants for 30 seconds to ensure that all participants experienced these perceived differences prior to testing.

Participants were asked to report the number of years (if any) that they have been involved in formal or informal music-making activities. This value was divided by age to provide a measure of musical experience (ME)

They then completed the Tolerance of Ambiguity (ToA) scale (Budner, 1962) – a widely used 16-item questionnaire designed to assess the degree of dis/comfort that an individual has in situations that lack information or that are complex or uncertain. The self-reported tolerance of ambiguity is measured using a scale from 1 (strongly disagree) to 5 (strongly agree) with higher scores indicating greater intolerance of ambiguity.

Finally, schizotypal personality was assessed using the shortened version of the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason, Linney, & Claridge, 2005). The inventory is a 43-item self-report questionnaire (dichotomous yes/no responses), comprising four analogue subscales of psychotic experiences:

Unusual Experiences (UE) (positive symptoms; perceptual aberrations and magical thinking); Cognitive Disorganisation (CD) (cognitive symptoms; poor attention, thought disorder; poor decision making, and social anxiety); Introvertive Anhedonia (IA) (negative symptoms; avoidance of intimacy and lack of pleasure from social and physical stimuli); and Impulsive Nonconformity (IN) (impulsive and antisocial symptoms; eccentric behaviours suggesting a lack of self-control). Higher scores indicate higher levels of schizotypy. Although all factors were examined, the factors related to positive schizotypy (i.e., UE primarily but also and CD) were hypothesised to be of particular interest.

4.3.6. fMRI data analysis

Image analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). For each participant the following pre-statistic processing was applied: motion correction using MCFLIRT (Jenkinson, 2002); slice-timing correction using Fourier-space time-series phase-shifting; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma=45.0s$). ICA-based exploratory data analysis was carried out using MELODIC (Beckmann, 2004), in order to investigate the possible presence of unexpected artefacts or activation. Following pre-statistics processing, a statistical analysis of time-courses was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001).

4.3.7. Individual and group-level GLM

For both runs, a task regressor was included for each of the 5 conditions. Each predictor covered the duration of 12 s composed of 5 trials (25 per run in total). Response periods and a variable representing the number of taps in each block were included as confounds, along with temporal derivative terms derived from each predictor. Contrasts were set to model condition-specific response as well as mean activation across all conditions: task (T) > baseline (B). Following an F test confirming significant continuous task-related response in all participants, 4 contrasts were used to further characterise positive and negative linear and quadratic response to our parametric manipulation with regressors: self (S) > other (O) [2 1 0 -1 -2]; O >

S [-2 -1 0 1 2]; middle (M) > extremes (E) [-2 1 2 1 -2]; and E > M [2 -1 -2 -1 2]. Fixed-effects analyses were then conducted using FEAT to estimate the average effects of all contrasts across runs within-participants.

Group-level mixed-effects analyses (treating subjects as random effects) were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) to estimate the average effects of interest (individual-level contrasts) for the group, with individual differences (IDs) added as covariates. Given the exploratory nature of the study, separate models were setup for each ID apart from O-LIFE where all subfactors were included as predictors in the same model, given previous evidence of factor overlap (Mason, Linney, & Claridge, 2005). Group Z (Gaussianised T/F) statistic images resulting from whole-brain voxel-wise comparisons were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$ (Worsley, 2001).

4.3.8. Network analysis

Functional networks with significant variance contributions to the dataset were identified by temporally concatenating the data from the 48 runs (2 per participant) into a 4D file that could be entered into a group ICA (Beckmann, 2004) as implemented in MELODIC (Version 3.13), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Data were decomposed into 20 spatially and temporally distinct components in order to represent robust large-scale networks (Beckmann et al. 2005; Greicius et al. 2007; Smith et al., 2009).

The 20 normalised component maps were visually inspected (in both spatial and frequency domains) and spatially cross-correlated with 10 intrinsic network templates to distinguish brain networks from artifactual components and identify canonical networks corresponding to components (Smith et al., 2009). The components that showed a moderate to good ($r > 0.30$) correlation with the templates were carried forward for further analysis.

To examine task-related temporal fluctuations in network activity following Clewett et al. (2014), the run-specific temporal responses time-course of each non-artifactual component were fit to each run's respective GLM design matrix. Following this

temporal regression, a component-specific t-statistic was calculated for each contrast by averaging the contrast of parameter estimates for the two runs and dividing this value by associated standard deviations, averaged across both runs. Consistency of these values across participants was examined for each component using a one-sample t-tests for mean ($T > B$; $B > T$), linear ($S > O$; $O > S$) and non-linear ($M > E$; $E > M$) contrasts (see Fig. X). To shed light on mean, linear and quadratic component modulation during the task, (Pearson, two-tailed) t-statistic values were correlated with individual difference measures (see Fig. X). Welch two sample t-tests on absolute resulting correlation values were conducted to test whether ICs included in the study were better predictors of mean, linear or quadratic contrasts.

Finally, we used a dual regression implemented in FSL to examine how individual differences predicted connectivity between network components and other parts of the brain (Beckmann et al., 2009). The procedure involved the following steps: group components were regressed against participants' preprocessed data to produce run-specific time-courses which were in turn used as predictors to generate corresponding spatial maps. These maps were averaged across runs to produce participant-specific components which could then be entered into a whole-brain, non-parametric regression, using FSL's randomise tool with previously described group-level GLMs (with individual difference covariates) as predictors. Five thousand permutations were carried out for each model and significant clusters corrected for multiple comparisons using threshold-free cluster enhancement, reported at $P < 0.05$, corrected (Smith and Nichols, 2009).

4.4. Results

4.4.1 Behavioural findings

Data from the agency task completed in the scanner were analysed to ensure that participants completed the task as expected. The mean number of actions per block was 40.35 (SD=6.52), mean number of tones per block was 42.34 (SD=4.4), and mean attribution rating (scaled from 0 to 1) was 0.54 (SD=0.2). Mean tap-tone synchrony (calculated as the correlation between Butterworth filtered tap and tone timings) was -0.97 (+/- 0.01). There was a tendency for participants to perform fewer

taps as the proportion of tones belonging to other increased, mean $r = -0.27$ ($SD=0.17$); this tendency, however, was non-significant for all but one participant (mean $p=0.34$, $SD=0.26$). The number of tones per block also did not vary significantly with condition, mean $r = 0.17$ ($SD=0.14$) (mean $p=0.4$, $SD=0.33$). Table 4.1 shows tap-tone correlation, the number of taps and tones per block for each of the five conditions (with associated standard deviations). Taken together, this indicates that the probability manipulation resulted in well-matched conditions that systematically varied in the proportion of self-other control over tones.

Table 4.1. Summary statistics by condition (C1 - C5) with data pooled over all participants. Standard deviation is presented within parentheses

	C1	C2	C3	C4	C5
Manipulation threshold	1	0.75	0.50	0.25	0
Tap tone correlation	1 (0.00)	0.72 (0.08)	0.52 (0.07)	0.28 (0.08)	0.02 (0.05)
Mean taps per block	42.80 (5.80)	40.78 (6.63)	40.15 (6.22)	39.06 (6.26)	38.93 (7.32)
Mean tones per block	42.80 (5.80)	43.43 (4.46)	44.65 (4.40)	43.16 (4.61)	39.07 (4.88)
Attribution	0.08 (0.13)	0.40 (0.23)	0.59 (0.24)	0.78 (0.19)	0.85 (0.17)
Misattribution	0.08 (0.13)	0.15 (0.23)	0.09 (0.24)	0.03 (0.19)	-0.15 (0.17)

Correlation between tap-tone asynchrony (calculated as synchrony but inverted for clarity) and attribution rating deriving from the post-scan agency task was used as the measure of between individual variation in agency performance (Perf), mean $r = .76$, $SD = .12$. Descriptive statistics (mean and standard deviation) and relationships among individual difference measures are shown in Table 4.2. In brief, O-LIFE sub-factors UE and CD were significantly correlated, indicating overlap, while IA and IN were negatively related. Though a general negative association was seen between Perf and OL factors, two-tailed significance was not reached in our sample. A non-significant positive trend was also observed between ToA and positive schizotypy (UE and CD), while the trend was negative in relation to Perf, ME and AS. ME was positively related to Perf and negatively associated with UE. The inverse correlation found between ToA and AS and their opposing trend in relation to Perf, UE and ME indicates that the ability to cope with ambiguity is associated with low ToA and high AS.

Table 4.2. Descriptive statistics and Pearson correlation matrix for individual difference measures

Variable	Descriptive stats		Pearson correlation matrix						
	Mean	sd	UE	CD	IA	IN	Perf	ToA	ME
Unusual experience (UE)	4.71	2.29							
Cognitive Disorganisation (CD)	3.71	1.55	0.71 ***						
Introvertive Anhedonia (IA)	5.21	1.41	-0.03	-0.15					
Impulsive Nonconformity (IN)	4.79	1.1	0.11	0.17	-0.42 *				
Performance (Perf)	0.76	0.12	-0.24	-0.26	-0.1	-0.32			
Tolerance of Ambiguity (ToA)	51.83	9.58	0.32	0.27	0.14	-0.07	-0.28		
Musical Experience (ME)	0.27	0.24	-0.39 *	-0.3	0.21	-0.18	0.44 *	-0.25	
Auditory Stream (AS)	7.75	5.62	-0.16	0.04	-0.01	-0.18	0.2	-0.45 *	0.31
n=24; * p<0.05, ** p<0.01, *** p<0.001 (two-tailed)									

4.4.2. ICA results

Nine out of 20 components showed a moderate to good ($r > 0.30$) correlation with network templates (Smith et al., 2009): they represented visual (VN:IC2, $r = .67$), default mode (DMN: IC3, $r = .48$; IC7, $r = .3$; IC15, $r = .41$), auditory (AN:IC4, $r = .67$), right-lateralised frontoparietal (rFPN:IC14, $r = .7$), left-lateralised frontoparietal (IC8, $r = .65$), cerebellar (IC16, $r = .37$), and sensorimotor (SMN: IC12, $r = .62$) components (see Fig. x). Based on previous findings one of the networks of interest was the salience (or executive control) network with nodes centred around the anterior insula and ACC; however no single component could be said to represent this network. Lowering the map threshold from $Z=4$ to 2.3 revealed that in our data this network was incorporated into both visual- and auditory-related components (IC2 and IC4 respectively). Given the absence of previous agency research using a network approach, all 9 components were tested. The 11 remaining components were deemed artifactual due to predominant activation in white matter, ventricles, or vasculature, head movements, or signal drop out.

4.4.2. Average task effects

Examining between-individual consistency of t-values derived from regressing IC time-courses onto respective run-specific GLMs using a one-sample t tests showed increased response during the task to be associated with IC4 (AN) and IC12 (SMN), while DMN-related ICs 3, 15 and 7 were strongly associated with baseline response. All ICs showed increased response for self compared to other (negative linear), though ICs 3, 5 and 16 did not reach significance. U-shaped (extremes (E) > middle (M)) quadratic response was associated with IC4 (AN), which included temporal,

insular and subcortical regions. These findings are presented in Fig. 4.3 alongside statistical maps (B) derived from mixed-effects group analysis for corresponding contrasts (A), allowing method comparisons to be made. Confirming a previous study (de Bezenac et al., under review), no ICs/networks or regions showed significant positive linear (other (O) > self (S)) or inverted U-shape quadratic (E>M) response in relation to the task. We used individual differences to explore between-individual variation in task-related neural response.

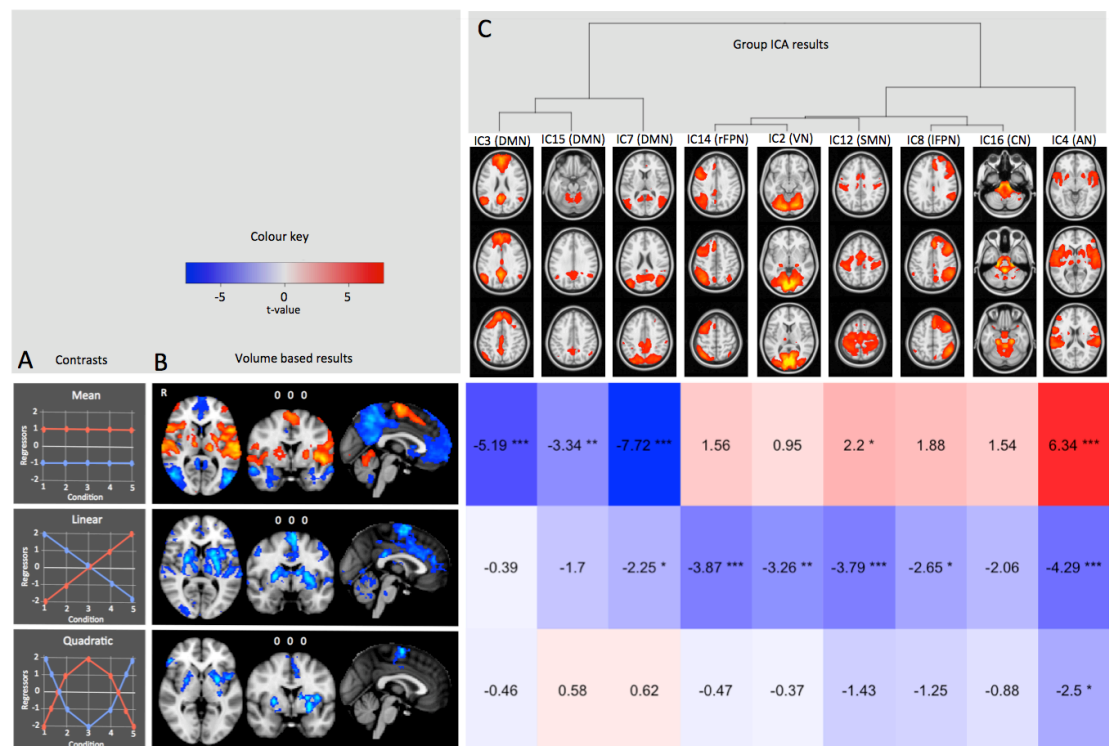


Fig. 4.3. Regions (mixed effects analysis results) (B) and group independent components (networks) (C) showing between-individual consistency (t-values) (lower C) in mean (task (T) > baseline (B); B > T), linear (self (S) > other (O); O > S) and quadratic (middle (M) > extremes (E); E > M) response to task manipulations (conditions 1 to 5) (A). The x axis is presented as a dendrogram, hierarchically clustered to facilitate interpretation. $n=24$; * $p<0.05$, ** $p<0.01$, *** $p<0.001$ (two-tailed).

4.4.3. Individual differences related to brain regions

Significant results for the GLMs with individual differences included as covariates may be seen in Table 4.3 for mean (task (T) < baseline (B); B>T), linear (S>O; O<S) and quadratic (M>E; E>M) contrasts. Only O-LIFE measures associated with positive schizotypy (i.e., UE and CD) modulated task-related response when controlling for other O-LIFE factors; no contrasts showed significant clusters with IA and IN as predictors. During baseline compared to task periods (B>T), CD

predicted increased temporal and frontal gyrus response while frontal pole response increased with Perf. In conditions where other had more control than self (O>S), occipital areas were more active as UE increased and middle frontal gyrus response for other increased with Perf.

Table 4.3. Brain regions with task-related response modulated by individual differences (ID). Mean (task (T) > baseline (B); B > T), linear (self (S) > other (O); O>S) and quadratic (middle (M) > extremes (E); E > M) response to conditions 1-5 was examined in relation to O-LIFE factors including unusual experience (UE) and cognitive disorganisation (CD), as well as task performance (Perf), tolerance of ambiguity (ToA), musical experience (ME) and auditory stream task (AS). Regions were defined by the Harvard-Oxford Cortical and Subcortical Structural Atlases and the Cerebellar Atlas in MNI152 space after normalization with FLIRT. P-values and n-voxels refer to the cluster. Hemisphere (H), brodmann area (BA), and MNI coordinates are provided for the most significant voxel within the cluster.

Contrast	ID	Region (Structures to which each cluster belongs to in %)	H	BA	n voxels	Z (max)	p-value	MNI coordinates			
									x	y	z
Mean											
B > T	CD	-- Middle Temporal Gyrus (30%), Posterior Inferior Temporal Gyrus (22%), Posterior Superior Temporal Gyrus (10%)	R	20	547	4.69	0.00395	52	-28	-20	
		-- Middle Frontal Gyrus (31%), Frontal Pole (18%)	R	45	519	3.61	0.0056	40	30	28	
B > T	Perf	-- Frontal Pole (13%), Frontal Orbital Cortex (5%)	L	10	731	3.69	0.000434	-20	58	2	
Linear											
O > S	UE	-- Occipital Pole (21%), Superior Lateral Occipital Cortex (19%)	L	19	429	3.6	0.0134	-22	-84	22	
O > S	Perf	-- Middle Frontal Gyrus (36%), Superior Frontal Gyrus (9%)	R	45	776	3.78	0.000212	42	30	46	
Quadratic											
M > E	UE	-- Postcentral Gyrus (18%), Central Opercular Cortex (13%), Precentral Gyrus (11%), Superior Temporal Gyrus (7%), Heschl's Gyrus (3%)	R	48	1147	3.85	1.13E-06	62	-6	16	
		-- Supplementary Motor Cortex (31%), Anterior Cingulate Gyrus (12%), Superior Frontal Gyrus (7%)	L	24	427	3.63	0.00842	-10	16	32	
M > E	CD	-- Cerebellum: Right Crus II (43%), Right Crus I (38%)	R	n/a	386	3.67	0.0157	40	-76	-42	
		-- Cerebellum: Left Crus II (52%)	L	n/a	413	3.53	0.0104	-6	-88	-36	
E > M	Perf	-- Anterior Cingulate Gyrus (22%), Precentral Gyrus (12%), Posterior Cingulate Gyrus (11%), Supplementary Motor Cortex (9%)	n/a	23	821	3.77	8.13E-05	0	-10	44	
		-- Precuneus Cortex (18%), Posterior Cingulate Gyrus (17%)									
M > E	ToA	Anterior Cingulate Gyrus (11%), Supplementary Motor Cortex (11%)	L	n/a	575	3.8	0.0015	-4	-40	48	
		-- Lateral Occipital Cortex (51%), Middle Temporal Gyrus (13%), Angular Gyrus (4%)	L	37	931	3.61	2.10E-05	-58	-66	14	
		-- Superior Parietal Lobule (32%), Postcentral Gyrus (22%)	R	5	416	3.39	0.0132	22	-54	64	
E > M	ME	-- Supramarginal Gyrus (32%), Postcentral Gyrus (12%), Parietal Operculum Cortex (10%), Planum Temporale (4%), Heschl's Gyrus (2%)	R	40	385	3.5	0.0217	68	-36	34	
		-- Central Opercular Cortex (17%), Insular Cortex (15%), Inferior Frontal Gyrus, pars opercularis (8%), Frontal Operculum Cortex (8%)	L	48	393	3.4	0.0193	-50	6	-4	
M > E	AS	-- Frontal Pole (63%)	R	46	408	3.58	0.0157	40	50	12	
E > M	AS	-- Frontal Pole (33%), Paracingulate Gyrus (22%), Superior Frontal Gyrus (5%)	L	10	951	4	1.88E-05	-20	60	22	
		-- Middle Frontal Gyrus (24%), Frontal Pole (23%), Superior Frontal Gyrus (10%)	L	9	554	3.76	0.00212	-26	42	34	

On the whole, individual differences included in the study (related to schizotypy, agency and ambiguity-processing) were better predictors of quadratic response to task manipulation (M>E; E>M), as indicated by the number of clusters reaching significance (see Table 4.3). These are presented in Fig. 4.4. Increased response in the middle of the self-to-other continuum (M>E) was predicted by UE in the precentral and postcentral gyri, superior temporal, supplementary motor and anterior

cingulate regions, and by CD in the cerebellum. This inverted U-shape pattern was also associated with ToA in cortical midline structures including the precuneus, the posterior and anterior cingulate gyrus as well as in the superior parietal lobule and lateral occipital cortex.

In contrast, increase response at the extremes of the self-to-other continuum ($E > M$) was predicted by Perf in the anterior cingulate gyrus, and by ME in the right supramarginal gyrus extending to Heschl's gyrus, as well as in a cluster between the central opercular and insular cortex. AS pointed in both directions, predicting increased right frontal pole response in the middle of the continuum and left frontal pole and paracingulate response at the continuum extremes compared to the middle ($E > M$).

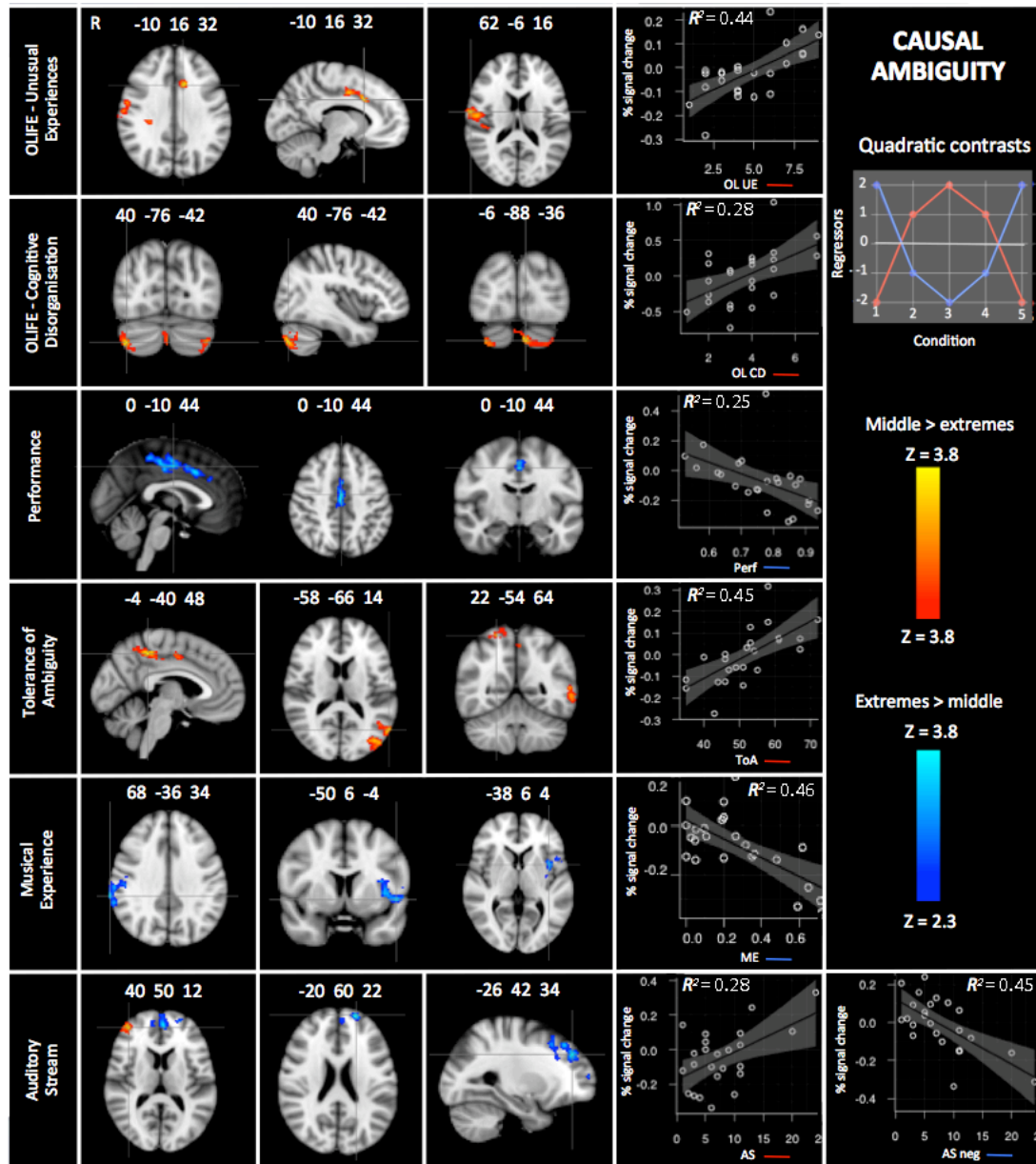


Fig. 4.4. Individual differences (ID) in brain response to quadratic contrasts (causal ambiguity: middle (M) > extremes (E); E>M), $Z > 2.3$, cluster corrected at $p = 0.05$. Scatterplots show participants' mean % signal change of voxels in significant clusters against each ID, with grey bands representing standard error. Statistical images were thresholded, are overlaid on the MNI-152 2mm brain with MNI coordinates (x,y,z) given for cross hair locations (peak voxels) and follow radiological convention, with the right hemisphere represented on the left side.

4.4.4. Individual differences related to group independent components

For mean task contrasts (T>B; B>T), significant positive correlation (increased response for task compared to baseline: T>B) was observed between IC2 (VN) and IA, $r(23) = 0.48$, $p = 0.01$. Negative correlation (B>T) was observed between IC3 (DMN) and AS, $r(23) = -0.42$, $p = 0.04$, and between IC14 (rFPN) and OL IN, $r(23) = -0.48$, $p < 0.01$. For linear contrasts (S>O; O>S), positive correlation

(increased response for other compared to self: O>S) was observed between IC14 (rFPN) and UE, $r(23) = 0.44$, $p = 0.03$, between IC2 (VN) and UE, $r(23) = 0.5$, $p < 0.01$, between IC2 (VN) and IN, $r(23) = 0.47$, $p = 0.02$, and between IC14 and ToA, $r(23) = 0.42$, $p = 0.04$.

As in the previous analysis, individual difference measures were better predictors of quadratic (mean absolute $r = 0.25$; sd $r = 0.3$) than mean (mean absolute $r = 0.15$, sd $r = 0.18$), $t = 3.7(121)$, $p = 0.0003$, or linear (mean absolute $r = 0.18$, sd $r = 0.19$), $t = 2.67(124)$, $p = 0.008$, component modulation. Results for the quadratic contrasts (M>E; E>M) are presented in Fig. 4.5. Components (x axis) and individual differences (y axis) have been hierarchically clustered to facilitate interpretation and p-values (represented by asterisks) are presented uncorrected for between-component comparisons, following previous procedures (Nomi & Uddin et al., 2015; Uddin et al., 2013). UE, CD and ToA predicted an increased response in the middle of the self-to-other continuum (M>E) in posterior nodes of the DMN (IC15) and VN (IC2) (which along with AN included salience network). UE also correlated positively with AN (IC4) and SMN (IC12) and ToA predicted increased response in the main DMN (IC3). In contrast, response in these networks/ICs was reduced in the middle of the continuum when predicted by Perf, ME and AS. More specifically, Perf predicted less SMN (IC12) response, while ME predicted was negatively related to VN (IC2), AN (IC4) and SMN (IC12). AS predicted decreased ambiguity-related response in DMNs and increased response in lFPN (IC8).

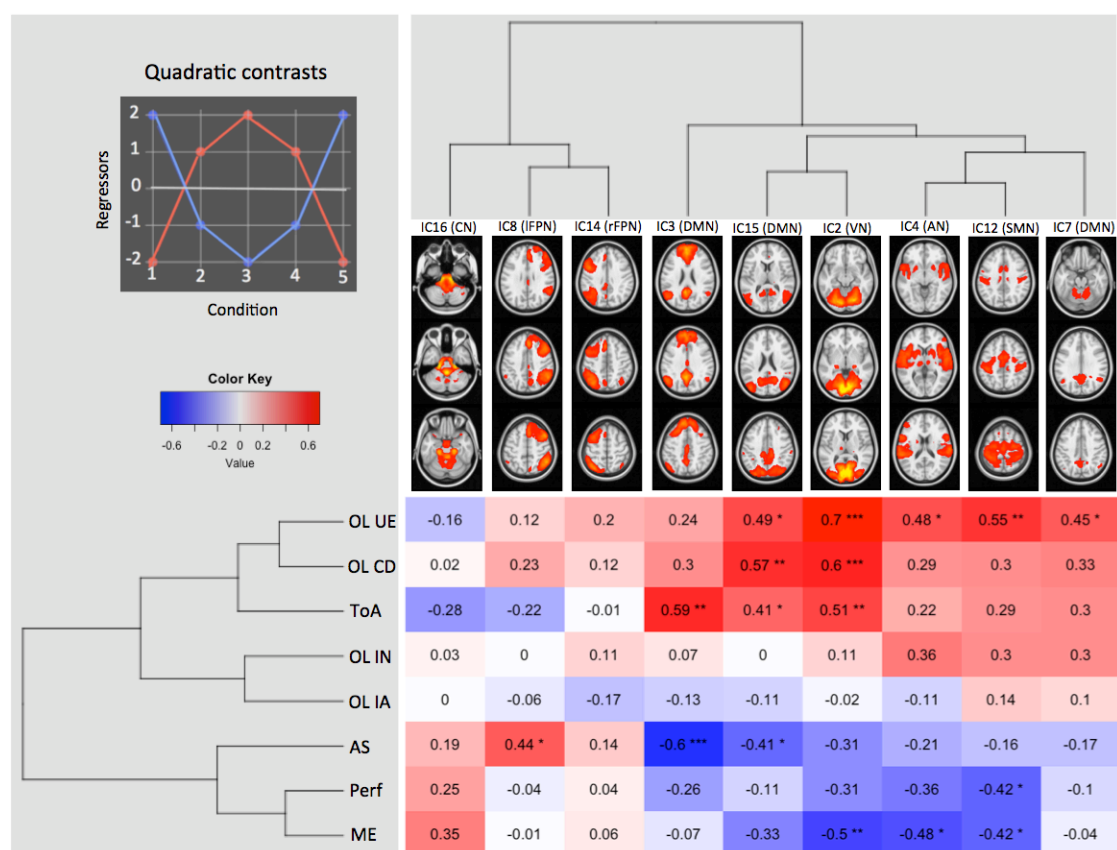


Fig. 4.5. Correlations between individual differences (y axis) and functional network connectivity estimates (x axis) associated with quadratic contrasts (middle (M) > extremes (E); E>M). X and y axes are presented as a dendrogram, hierarchically clustered to facilitate interpretation. $n=24$; * $p<0.05$, ** $p<0.01$, *** $p<0.001$ (two-tailed).

Results of the dual regression analysis which tested whether individual differences predicted connectivity between ICs and other brain regions (within grey matter voxels), showed that UE predicted increased functional coupling between IC14 (rFPN) and a small cluster (36 voxels: MNI coordinate of max: $x=22$, $y=-54$, $z=64$) in the right middle temporal gyrus, posterior division (rMTG) ($P < 0.05$, corrected) (Fig. 4.6). No other individual difference measures showed significant IC connectivity clusters after correcting for between-voxel comparisons.

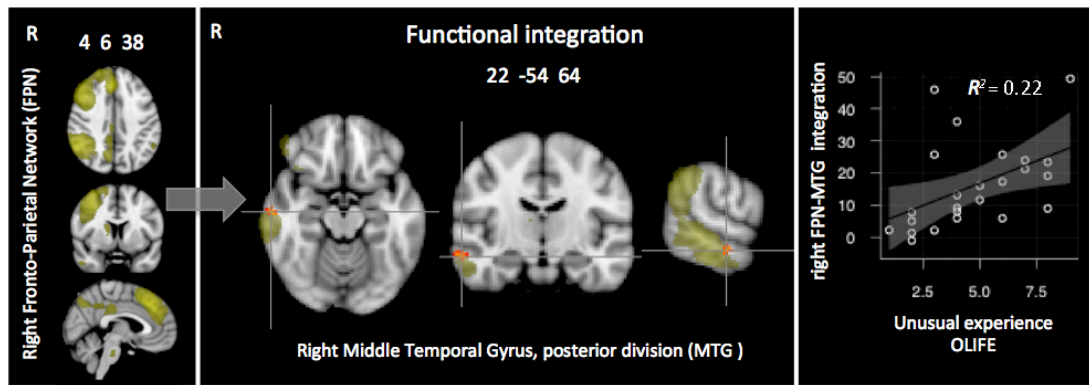


Fig. 4.6. Unusual experiences (O-LIFE) predicting increased functional connectivity between the right fronto-parietal network (light green) and right middle temporal gyrus, posterior division (red to yellow). Threshold-free cluster enhancement was used for multiple comparisons (grey matter voxels) correction. Voxels shown passed a corrected threshold of $P < 0.05$. Images follow the radiological convention, with the right hemisphere represented on the left side. The Statistical image is overlaid on the MNI-152 2mm brain with MNI coordinates given for the cross hair location.

4.5. Discussion

This study explored brain behaviour-relationships associated with self-other processing. We did this by manipulating the probability that actions of self or other would generate tones, examining how individual differences previously associated with this process predicted neural response when tone control was manipulated across the self/other dimension. We were particularly interested in conditions of increased causal ambiguity, where self- and other-generated tones were equally likely. It is in these challenging conditions, which resemble complex social encounters in this respect, that we expected response variation to be explained by selected individual differences.

4.5.1. Behavioural results

Relationships between these variables broadly pointed in predicted directions, with overall task performance reducing with schizotypy and ToA and increasing with musical experience and AS. Though task performance was positively correlated with ME, in line with our previous findings, its negative correlation with UE did not reach significance. In this previous study (de Bezenac et al., 2015) it was in the middle of the self-to-other continuum that hallucination proneness (and ME) predicted increased misattribution in line with the proposed role of ambiguity in agency. That a

measure of overall task performance (across the entire self-other continuum) was used in this study may explain the weakened effect of positive schizotypy.

Though some findings from the whole-brain univariate analysis and ICA related to linear response where control belonged more to self or to other, individual difference measures included in the study more effectively explained neural variation related to causal ambiguity, as indicated by the number significant findings (see Table 4.3) and increased correlation values associated with quadratic contrasts in the ICA results. This suggests that challenging situations with less information for self-other differentiation accentuates the effects of individual difference traits, maximising the need for perceptual inference (Schmack et al., 2015; de Bezenac et al., 2015; Gallagher, 2013; Fukushima et al., 2013). Increased ambiguity-related neural variation between individuals may also explain the absence of increased response to ambiguity (inverted U-shape) in our overall group results reported in de Bezenac et al. (under review) (see Fig. 4.3).

4.5.2. Univariate analysis results

As anticipated, when schizotypy factors were included as additional explanatory variables, it was positive (UE) but not negative (IA) schizotypy that predicted task-related response. This accords with models associating unusual experiences including hallucinations and delusions with agency deficits (Frith, 2005; Jeannerod, 2009). UE specifically predicted increased response in the middle of the continuum in a right inferior frontal and temporal region (including the post- and precentral gyrus, STG, and Heschl's gyrus), previously implicated in auditory stimulation and the cognitive control of spoken language (Geranmayeh et al., 2014). Hallucinatory experiences have previously been linked to activation of this region in the absence of external auditory stimuli (Lawrie et al., 2002; Woodruff et al., 1995; Shergill et al., 2000; Dierks et al., 1999). Response also increased in SMA (extending to ACC) – a key region of the motor system previously associated with the sense of agency (Tsakiris, Longo & Haggard, 2010; Farrer et al., 2003; Nahab et al., 2011) and, more specifically, ambiguity in agency (Fukushima et al., 2013), as well as with auditory verbal hallucination (Raij & Riekk, 2012; Zhou et al., 2007). Interestingly, there are also reports that lesion-induced disruptions in this region give rise to experiences of alien control (Mellor, 1970:18; Goldberg, Mayer, & Togli, 1981:684-685).

With other O-LIFE factors controlled for, CD predicted increased cerebellar response during causal ambiguity. In addition to basic motor control, the cerebellum is increasingly thought to play a central role in multiple higher-level cognitive functions (Timmann & Daum, 2007) implicated in schizophrenia-related disorders (Picard et al., 2008; Konarski et al., 2005). In addition to its involvement in externally attributed agency (Blakemore, Wolpert & Frith, 1999), the cerebellum has been linked to error-related cognitive control (Ide and Chiang-shan, 2011), prediction of movement outcomes (Fuentes and Bastian, 2007), working memory (Akshoomoff, and Courchesne, 1992), cognitive flexibility (De Bartolo et al., 2009; Kim, Ugurbil, and Strick, 1994) and social cognition (Van Overwalle et al., 2014) – domains likely to require processing of situations where causal ambiguity features.

Task performance (Perf) predicted reduced ambiguity-related response in the posterior and anterior cingulate gyrus, in contrast to ToA which correlated with increased response in precuneus and cingulate regions. Our findings suggest that these midline structures may be key to how ambiguity, as it occurs in self-other differentiation, is processed. This is supported by previous findings implicating the cingulate gyrus (particularly the anterior division) in ambiguity related to both agency (Fukushima et al., 2013) and decision-making (Botvinick et al., 2001; Stern et al., 2010; Critchley et al., 2001). Consistent with our results, Krain et al., (2008) found that intolerance of uncertainty (a measure similar to ToA) predicted increased response in cingulate regions during a decision-making task, while high tolerance and less anxiety deactivated the same regions in response to uncertainty. Other domains relevant to ambiguity and agency associated with this region include monitoring stimuli for errors (Carter et al., 2007; Bush, Luu, and Posner, 2000), verbal working memory (Metzak et al., 2011), attention to willed actions (Paus, 2001), external action attribution (Farrer and Frith, 2002), and socially-driven interactions (reviewed in Lavin et al., 2013). As key nodes of the DMN, increased activation in posterior midline structures has been linked to mind wandering and self-referential processing, while relative deactivation has been linked to demanding tasks involving externally-focussed attention (being “on task”) including working memory and meditation (Brewer et al., 2013; Sperduti et al., 2012). Therefore, these regions are considered to be directly involved in regulating the focus of attention (Leech and

Sharp, 2014). Neuroimaging investigations also suggest that midline structures have a significant part to play in pathogenesis of schizophrenia (reviewed in Adams & David, 2007). Though Adams and David's review (2007) shows evidence for both hypo- and hyper-activation, increased ACC activation has been observed during auditory hallucinations (Shergill et al., 2000). The response patterns we found in relation to individual difference variables in all medial regions supports a hyper-activation model of positive symptoms in relation to causal ambiguity.

ME predicted reduced ambiguity-related response in a left temporal region that included the insula, as well as in the right IPL (supramarginal gyrus more specifically). Prior evidence indicates that the latter is activated during multiple forms of social cognition (reviewed in Decety & Lamm, 2007; Wible, 2012), including theory of mind (Saxe and Kanwisher, 2003) and agency particularly related action attribution to external causes (David et al., 2007; Blakemore et al., 2002; Farrer et al., 2003). Neuroimaging studies of positive symptoms of schizophrenia show over-activation in this region during agency tasks, providing a neural explanation of the associated tendency of attributing self-produced actions/thoughts to external causes (Farrer et al., 2004; Spence et al., 1997; reviewed in Wible, Preus, Hashimoto, 2009). Interestingly, reduced response predicted by ME found in this region partially overlapped with the postcentral region that increased with UE.

4.5.3. Network analysis results

Our task-related ICA findings allowed us to go beyond pinpointing single brain regions involved in agency and related behaviour. We found that positive schizotypy (UE in particular but also CD) predicted increased ambiguity-related recruitment of the DMN. This is consistent with prior findings indicating that schizophrenic patients have difficulties in deactivating DMN regions during tasks (Williamson and Allman, 2012; Whitfield-Gabrieli et al., 2009). Other studies specifically connect severity of hallucinations and delusions to altered functional connectivity of the DMN (Camchong et al., 2011; Rotarska-Jagiela et al., 2010). This, it has been argued, may reflect a loss of contact with relevant external stimuli and a difficulty in reallocating neural resources in challenging conditions (Smallwood et al., 2008; McKiernan et al., 2003). That the main DMN component was found to correlate with both ToA and AS (in opposite directions) in this study, suggests that ambiguity processing during

agentic considerations might involve DMN regulation. There is prior evidence that task-related deactivation of the DMN is accentuated by task difficulty and performance accuracy (Harrison et al., 2011; Gilbert et al., 2012; Polli et al., 2005). In relation to the latter, however, the negative trend predicted by task performance did not reach significance.

In addition to DMN recruitment, UE predicted increased ambiguity-related engagement in visual, auditory and sensorimotor networks. Brain regions associated with these networks have also previously been implicated in schizophrenia (Butler, Silverstein, Dakin, 2008; Rapin et al., 2010; Lawrie et al., 2002; Woodruff et al., 1995; van den Heuvel et al., 2010; Shergill et al., 2000). This may reflect motor-related ‘over-perceptualization’ that can lead to hallucinations (Allen et al., 2008). In contrast, ME again predicted reduced response in the visual, auditory and sensorimotor networks, generally pointing in the same direction as task performance and AS, and in the opposite direction to UE and ToA. The ME-related neural response patterns found in both analyses are consistent with previous behavioural results showing ME to be related to reduced misattribution particularly in ambiguous conditions (de Bezenac et al., 2015). They are also in line with findings showing music-training-induced neuroplasticity in multiple sensorimotor, auditory and language-related pathways (François et al., 2015; Chen et al., 2012). Together, our behavioural and imaging findings imply that practice in challenging ambiguous settings involving the intricate coordination of one’s own actions with those of others may improve self-other processing abilities, which are thought to be impaired in schizophrenia (Frith, 2005; Jeannerod, 2009). This is supported by prior work relating long-term music training to improvements in working memory (George & Coch, 2011) and attentional control (Helmbold, Rammsayer, & Altenmüller, 2005; Lee, Lu, & Ko, 2007; Moreno & Besson, 2006). Indeed, precedents for practice-induced changes have been observed in a number of domains relating to executive function (Hussey & Novick, 2012; Manly & Murphy, 2012). Clearly more direct testing with relevant clinical populations is required to support this contention. Future work could explore whether experience in (musical and non-musical) ambiguous settings results in improvement of attribution accuracy and its implications for symptom severity.

4.5.4. Dual regression results

Though FPN recruitment was not directly modulated by UE, our dual regression results showed that UE predicted increased functional integration between the rFPN and a cluster in the right MTG during the task. This region has been previously implicated in positive symptoms of schizophrenia in a number of studies. In their examination of auditory hallucination, for example, Woodruff et al., (1997) found that schizophrenia patients showed increased response to external speech in the right MTG, which correlated with hallucination severity. Structural asymmetries have also been noted, with hallucination severity predicting reduced left hemisphere volumes in both the MTG and STG with right MTG being significantly larger than the left (Onitsuka et al., 2014; Hu et al., 2013; Kuroki et al., 2006; Tang et al., 2012). Our functional connectivity findings add to this picture by suggesting that these group differences may be more specifically related to altered interaction between the MTG and other regions associated with the right frontoparietal attention network.

4.5.5. Increased and decreased response

Examining overall trends from findings derived from the whole-brain univariate analysis and task-related ICA, a generalised increase in ambiguity-related response correlated with UE, CD and ToA in multiple regions and networks, in contrast to the decrease in response predicted by task performance and ME. (AS pointed in both directions, reducing in left frontal regions of the DMN and increasing in a right frontal region and rFPN.) Elevated-activation has previously been related to cognitive load and inhibitory control deficits in schizophrenia (Brandt et al., 2014; 2015; Clark, 1996), prolonged mental fatigue (Ishii et al., 2013), anxiety in the absence of relevant information (Rigoli et al., 2013) and during social processing (Hall et al., 2008; Mukherjee et al., 2013), and poor performance in working memory tasks (Engström, Landtblom, and Karlsson, 2013). For example, Driesen et al. (2013) found that schizophrenia-like symptoms induced through ketamine were associated with increased global functional connectivity during resting-state fMRI.

In contrast, neuronal inhibition (Frankenstein et al., 2003), thought to play a central role in working memory among other cognitive functions (Rosen & Engle, 1998; Tomasi et al., 2006), has been associated with accurate task performance (Polli et al., 2005; Engström, Landtblom, & Karlsson, 2013) and processing skills associated with

ambiguity in language, such as the suppression of possibilities related to a target concept in semantic reasoning (Faust & Gernsbacher, 1996; Mirman & Graziano, 2013). Decreases in neural response after practice reported in a wide range of cognitive tasks has been linked to automatisisation (Van Raalten et al., 2008) and the capacity to perform a number of working memory tasks simultaneously (Ramsey et al., 2004). Overall response reductions may reflect a strategy of selectively suppressing internal and external stimuli in causally ambiguous contexts or increased practice-induced efficiency and automatisisation (Van Raalten et al., 2008; Jäncke et al., 2000). This could be tested using a design that allows response fluctuations to be investigated at smaller time-scales.

4.5.6. Conclusions

In conclusion, findings from this exploratory fMRI study suggest that a greater understanding of how individuals respond to causally ambiguous contexts can shed light on mechanisms of self-other processing and on phenomena such as hallucinations previously associated with agency deficits. Though our study explored brain-behaviour relationships in a non-clinical sample, findings relating positive schizotypy and an inability to tolerate ambiguity to increased neural response during causally ambiguous conditions in a number of regions and networks allows specific predictions to be made in future research comparing clinical and non-clinical groups. Furthermore, the functional patterns found in relation to task performance and ME, if confirmed, raise the possibility that the ability to differentiate self from other can be refined by engaging in intrinsically motivating activities that blur self-other boundaries through intricate joint behaviour. At a neural level, this may be reflected in decreased response linked to functional efficiency. A greater understanding of the process of differentiating self from other during development and the extent to which this ability can be honed through practice in later life could lead to new strategies for promoting resilience to symptoms of psychosis.

4.6. Acknowledgements

The authors would like to acknowledge the Institute of Psychology Health and Society, University of Liverpool for funding data collection and a studentship. We thank David Clewett for his guidance with the data analysis.

4.7. References

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CHAPTER 5

Agency performance modulates resting-state variation in prefrontal brain regions

[de Bézenac, C., Sluming, V., Corcoran, R. (under review). Agency performance modulates resting-state variation in prefrontal brain regions. *Neuropsychologia*]

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5.1. Abstract

Individuals differ in their ability to distinguish the effects of own from others' actions. For example, difficulties in self-other differentiation have been linked to positive symptoms of schizophrenia such as hallucinations, with causally ambiguous situations proving a universal challenge. Indeed, difficulties in this area have been shown to characterise non-clinical samples who self-report higher levels of positive schizotypy. The goal of the present study was to examine relationships between individual differences in resting-state functional connectivity and self-other attribution performance. Fifty-five healthy adults completed a resting-state fMRI scan and a task that systematically modulated the probability that finger taps of self versus other would generate auditory tones. Using group independent component analysis (ICA) and dual regression, we found that connectivity between prefrontal networks and other brain regions increased as overall performance decreased and misattribution biased towards other increased. These findings shed additional light on the neural mechanisms of agency, emphasising that connectivity with prefrontal networks play an important role in self-other differentiation.

Keywords: Agency; prefrontal cortex; ambiguity; resting-state fMRI; independent component analysis

Highlights

- Agency performance modulated resting-state activity
- A medial prefrontal network extended into other regions with lower agency abilities
- Between-network connectivity increased with bias and lower performance

5.2. Introduction

Our waking day is filled with encounters that involve coordinating our own thoughts and behaviours with those belonging to other individuals. A prerequisite for doing this is the ability to distinguish acts of the ‘self’ from those of ‘others’ by forming accurate predictions about action-outcomes (Wolpert et al. 1995; Frith, 2005; Wegner, 2003). Even in the absence of others, we think about, and attempt to work out who is responsible for events that have or will take place. The sense of agency, the feeling that ‘I am in control of my thoughts, actions and their consequences’ (Gallagher, 2000) is a complex and multifaceted phenomenon that can be influenced by sensorimotor processes as well as by individuals’ mental and emotional states; their intentions, expectations and biases (Synofzik, Vosgerau & Newen, 2008; Dijksterhuis et al., 2008; Farrer et al., 2008; Sato, 2009; Synofzik, Thier, & Lindner, 2006; Wegner, 2003).

Evidence suggests that individuals differ in their ability to objectively distinguish between events caused by self from those caused by other individuals. Difficulties associated with this fundamental skill are thought to be a core cognitive feature of schizophrenia, reflected in positive symptoms like delusions of control and auditory verbal hallucinations (Waters et al., 2012; Ditman & Kuperberg, 2005; Frith, 2005;

Jeannerod, 2009; Spence et al., 1997). Performance discrepancies have also been shown in non-clinical samples (Sugimori, Asai, & Tanno, 2011; de Bezenac et al., 2015). For example, de Bezenac et al. (2015) found that accuracy in assessing the proportion of self-other control over auditory events decreased with hallucination proneness and, as anticipated, increased with music-making experience. This pattern of results was accentuated by task difficulty, i.e., in conditions where tones were as likely to belong to self as to other. Agency performance is therefore also determined by how an individual's previous experiences and expectations and cognitive biases interact with external factors (Wegner, 2002; 2003), such as the amount of prior information available to facilitate this decision-making.

Previous neuroimaging studies into sense of agency have examined brain activity as participants performed attribution tasks in the scanner. For example, studies have compared response to unaltered visual feedback of action with feedback that has been distorted using delay (e.g., Leube et al. 2003) or spatial displacement (e.g., Farrer et al. 2003; David et al. 2007). These paradigms have implicated a number of disparate regions involved in sensorimotor control and multimodal integration (for reviews see Sperduti et al., 2011, David et al., 2008). Some regions, such as the insula, display particular sensitivity to clearly self-produced outcomes (Farrer et al., 2003). However, most other implicated regions have been primarily associated with action-outcome discordance typical of externally generated stimuli, though some have also shown sensitivity to self-agency (Renes et al., 2015). These include the inferior parietal lobe (Farrer et al., 2003; Chaminade & Decety, 2002), extrastriate body area (EBA) (David et al., 2007), medial and dorsolateral prefrontal cortex (Pfeifer, Lieberman, & Dapretto, 2007; Schnell et al., 2007), and cerebellum (Blakemore et al., 1999; 2002).

Patients experiencing the positive symptoms of schizophrenia have shown over-activation of the inferior parietal lobe (primarily associated with external causes) when performing attribution tasks (Spence et al., 1997; Jardri et al., 2011; Farrer et al., 2004). However, it is not yet clear how neural differences between individuals directly relate to agency performance. Increasing evidence suggests that inter-individual variation seen in the broad patterns of activation is meaningfully associated with cognitive and behavioural factors that constrain real world function

(Bassett et al., 2009, van den Heuvel et al., 2009).

FMRI studies have examined individual differences in neural response, not only during experimental tasks, but also during so called ‘resting-state’ – in the absence of an explicit task. Resting-state networks (RSN) have been shown largely to correspond to regions that are co-activated during the performance of specific tasks and can provide complementary information about brain function, avoiding confounds related to completing a task (Smith et al., 2009). Emerging findings suggest that the temporal and spatial organisation of such networks have behavioural and clinical relevance (for reviews see Greicius, 2008; Zhang and Raichle, 2010) and remain relatively stable across time within individuals (Shehzad et al., 2009; Guo et al., 2012). RSN patterns in neurologically typical individuals have been associated with a number of cognitive functions relevant to agency, including working memory (Gordon et al., 2014; Hampson et al., 2006), attentional control (Kelly et al., 2008), fluid reasoning (Cole et al., 2012) and theory of mind (Buckner & Carroll, 2007).

Network-based methods exploring co-activating areas have also been effective in highlighting neural differences between people with schizophrenia and matched controls (reviewed in Williamson and Allman, 2012; Karbasforoushan & Woodward, 2012). For example, severity of hallucinations and delusions were shown to correlate with aberrant functional connectivity in the default-mode network (DMN) (Rotarska-Jagiela et al., 2010), a set of brain regions associated with self-referential processing (Greicius et al., 2003; Christoff et al., 2011) and aspects of social cognition (Mars et al., 2012) including source attribution (reviewed in Northoff et al., 2006). The relationship between networks has also been shown to be clinically significant. For example, the anti-correlation typically observed between the DMN (the medial prefrontal area in particular) and the central executive network (CEN) (Wiebking et al., 2014), has been implicated in processes of self-other discrimination and shown to be attenuated in individuals at risk for psychosis (Spaniel et al., 2015; Wotruba et al., 2013). It has been argued that such neural differences may explain observed misattributions of internally or externally generated stimuli and that resting-state variation may play an important role in determining the sense of agency (Robinson, Wagner & Northoff, 2015).

Despite a shift towards considering networks as opposed to isolated regions as the unit of analysis in elucidating neural processes (Friston, 2011; Meehan & Bressler, 2012), network accounts of agency are scarce (David et al., 2007; David, Newen & Vogeley, 2008; Robinson, Wagner & Northoff, 2015). This line of research, however, has the potential to shed additional light on the functional relationships between brain regions previously implicated in self-other differentiation and the processes leading to agency difficulties and symptoms thought to be related to this facility. The current study aims to shed additional light on self-other processing by examining the relationship between performance on an agency task and functional connectivity in resting state fMRI. More specifically, we assessed the ability of 55 participants to identify the proportion of auditory tones resulting from finger taps belonging to self as opposed to ‘other’ (composed of randomised taps of self; see de Bezenac et al., 2015), as well as the extent to which misattribution towards other increased in the most challenging ambiguous conditions. These measures were used to predict functional differences both within- and between-networks using a data-driven approach involving group independent component analysis (ICA) and dual regression (Beckmann & Smith, 2005; Beckmann et al., 2009; Filippini et al., 2009).

Given the limited scope of prior research on functional connectivity and agency, the current study had a number of objectives: to (1) determine whether patterns of functional connectivity are associated with individual differences in overall task performance and in ambiguity-related misattribution; (2) examine whether such differences are associated with RSNs composed of regions previously implicated in agency tasks; and (3) investigate how individual differences in agency performance might predict alterations in either the connectivity of RSNs with other brain regions or other large-scale RSNs. Our hypothesis was that between-individual variation in functional connectivity during rest would be associated with agency performance measures and, more specifically, in the light of previous clinical evidence, that DMN nodes would be implicated. However, based on the lack of prior research in this area, our investigation was more exploratory with regard to how exactly such individual differences would be expressed.

5.3. Methods

5.3.1. Participants

The study sample initially consisted of 57 right-handed participants with a mean age of 25 years (SD = 8; range, 19–50). Participants were recruited from the student and staff population at the University of Liverpool. All participants reported normal or corrected-to-normal vision, normal hearing and somatosensory perception. No participants reported histories of mental or neurological illness. Two participants were excluded prior to statistical analysis due to incidental neurological abnormalities, leaving a final sample of 55 participants (28 females). All participants gave written informed consent as part of a protocol approved by the ethics committee of the University of Liverpool.

5.3.2. Imaging protocol

Participants completed a resting-state scan: they were asked to relax with their eyes closed for a duration of six minutes. Scans were obtained using a Trio 3.0 Tesla (Siemens, Erlangen, Germany), whole body MRI system, equipped with an eight-channel phased array head coil. Foam padding and head restraints were used to minimise head movement during imaging. Each scan consisted of 197 contiguous EPI functional volumes (TR = 2000 ms; TE = 25 ms; flip angle = 90°, 32 slices, matrix = 64 x 64; FOV = 192 mm; acquisition voxel size = 3.5 mm³). Before preprocessing these functional data, the first eight volumes of each run were automatically removed to allow for magnetic stabilization, leaving 180 usable volumes. To facilitate co-registration and normalization of these functional data, we also acquired a high-resolution T1-weighted magnetization prepared gradient echo sequence from each participant that lasted 12 minutes (TE 5.57ms, TR 2040 ms, flip angle 8°, FOV=256×256 mm², 176 slices, voxel size 1×1×1 mm³).

5.3.3. Behavioural task

Following the scanning session, participants completed a computerised agency task previously described in de Bezenac et al., (2015). Briefly, participants were asked to perform series of irregular taps (“like Morse code”) using their right index finger whilst listening to a sequence of tones on headphones. Tones either resulted from the participant’s actions (self) or from the actions of ‘other’, which consisted of the

previous 50 inter-tap intervals performed by the participant played back in a random order. The probability that self- or ‘other’-generated taps would produce tones was manipulated in 10 equal steps corresponding to 10 conditions, allowing a continuum ranging from tone control belonging fully to self (C1) to control belong fully to other (C10). In the middle of the continuum (C5, C6), the probability of self- and other-generated tones was equal, making self-other attribution more ambiguous. After a 3-minute practice session, each participant completed a total of 50 trials made up of 5 repetitions of each of the 10 conditions presented in a pseudorandom order (consecutive conditions were not presented consecutively). After each trial, consisting of 10 seconds of tapping, participants were asked to assess the proportion of control that they felt belonged to self versus to other along a continuum, using a computer mouse. The task took approximately 15 minutes to complete and was preceded by a 3-min practice session allowing 50 participant tap intervals to be recorded and used in non-self taps following randomisation. A schematic representation of the experimental paradigm is provided in Fig. 5.1 (left).

5.3.4. Behavioural variables

Overall performance (OP) was calculated as the correlation between participants’ attribution ratings (subjective locus of control) ranging from self to other and tap-tone asynchrony (objective locus of control). The latter was computed as the correlation between Butterworth filtered time-series of tap and tone onsets. A high correlation thus indicated that the subjective locus of control experienced by the participant matched the actual or objective locus of control instantiated in the task.

Misattribution (attribution error) was calculated as the difference between attribution rating (ranged between 0 and 1) and tap-tone asynchrony (also ranged between 0 and 1). Given that misattribution has been shown to peak in the middle of the self-to-other continuum (C5-C6) (de Bezenac et al., 2015), we represented ambiguity-related misattribution (AM) as the slope (b_1) of a regression line predicting misattribution by pooling conditions 1 and 10, 2 and 9, 3 and 8, 4 and 7, and 5 and 6. Positive values represent misattribution biased towards ‘other’ in ambiguous conditions (the middle as opposed to the extremes of the self-to-other continuum) with negative values indicating ambiguity-related misattribution biased towards self.

5.3.5. Image preprocessing

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing steps included motion correction (Jenkinson et al., 2002), non-brain removal (Smith, 2002), spatial smoothing (FWHM 5mm), grand-mean intensity normalisation, highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma=55.0s$). Registration to high-resolution structural and Montreal Neurological Institute (MNI) 152 stereotactic space (2 mm) images was carried out using default settings in FLIRT and a linear transformation with 12 degrees of freedom (Jenkinson & Smith, 2001, Jenkinson et al., 2002).

5.3.5. Within-network connectivity: dual regression ICA

The overall group preprocessed data consisting of 55 participants were temporally concatenated and entered into an ICA using MELODIC (Version 3.13) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC>) in FSL. Data were decomposed into 20 spatially and temporally distinct components in order to represent robust large-scale networks (Beckmann et al. 2005; Greicius et al. 2007; Smith et al., 2009). Visual inspection (Kelly et al., 2010) of these group-level ICs was used to identify those best representing previously identified networks (Laird et al., 2011; Smith et al., 2009), while components that did not match these networks were considered noise or artifacts such as movement, white matter, or ventricles. Spatial cross-correlation were also conducted to confirm IC-network associations.

Non-artifactual ICs were then compared to participant-specific timecourses and spatial maps using dual regression (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/DualRegression>). This involved: (1) regressing the group-spatial-maps into each participant's functional dataset to give a set of time-series; (2) regressing these time-series into the same dataset to get a participant-specific set of spatial maps; and (3) comparing the spatial maps across participants to look for positive and negative differences predicted by the behavioural variables (after accounting for mean group connectivity). Non-parametric permutation testing was carried out as part of the latter (step 3) using the randomise tool in FSL (5000 permutations) and resulting statistical maps were thresholded using threshold-free cluster enhancement with an alpha level of .05 (corrected). Following studies using

similar procedures (Uddin, Supekar, & Menon, 2013; Nomi & Uddin, 2015), correction for multiple component testing was not applied.

5.3.6. Between-network connectivity: FSL Nets

Between-network differences in functional connectivity were examined using the FSL Nets package implemented in Matlab (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets>). This analysis involved correlating participant-specific time-series from the dual regression (step 1) for each IC pair (Smith et al., 2010). Behavioural variables were then used to predict full and partial correlation values using randomise (5000 permutations).

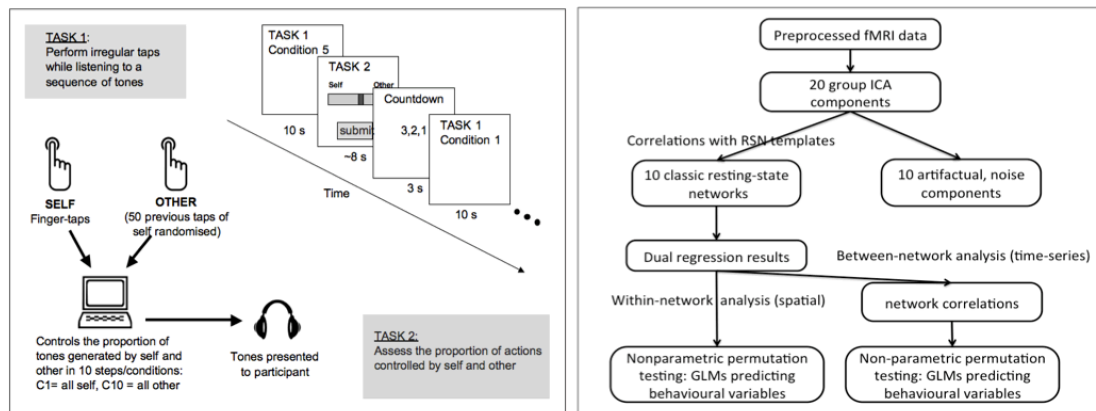


Fig. 5.1. Behavioural task depiction (left) and processing pipeline for resting-state fMRI data (right).

5.4. Results

5.4.1. Behavioural data

The data was found to be suitable for the proposed analyses, without floor or ceiling effects and with scores varying sufficiently across the group of participants. The 55 participants had a mean OP (r) score of 0.77 (SD = 0.1, range = 0.51 to 0.94) and a mean AM (b_1) score of 0.33 (SD = 0.2, range = -0.08 to 0.73). Confirming previous results (de Bezenac et al., 2015), the positive AB score in all but one participant indicates a general bias towards other in the middle of the self-to-other continuum. Given the possible effect of age on temporal discrimination implicated in agency and resting state networks connectivity (Ferreira & Busatto, 2013), we tested the relationship between age and our variables of interest (OP; AM). OP did not correlate with age ($r(53) = 0.04$, $p=0.73$) and neither did AM ($r(53)=0.06$, $p=0.64$).

5.4.2. Group ICA

Of the 20 ICs extracted from the group of 55 participants, 10 were determined to be artifactual, representing cerebral spinal fluid, ventricles, head motion, signal drop-out and white matter response. The 10 remaining ICs seen on Fig. 5.2 were entered into the dual regression analysis and corresponded to default mode (IC1, $r = .75$; IC4, $r = .36$), right frontoparietal (IC2, $r = .59$), visual (IC3, $r = .66$), sensorimotor (IC5, $r = .59$), auditory (IC6, $r = .6$), dorsal attention (IC7, $r = .45$), left frontoparietal (IC8, $r = .65$), executive control (IC9, $r = .67$), and frontal (IC10, $r = .52$) networks.

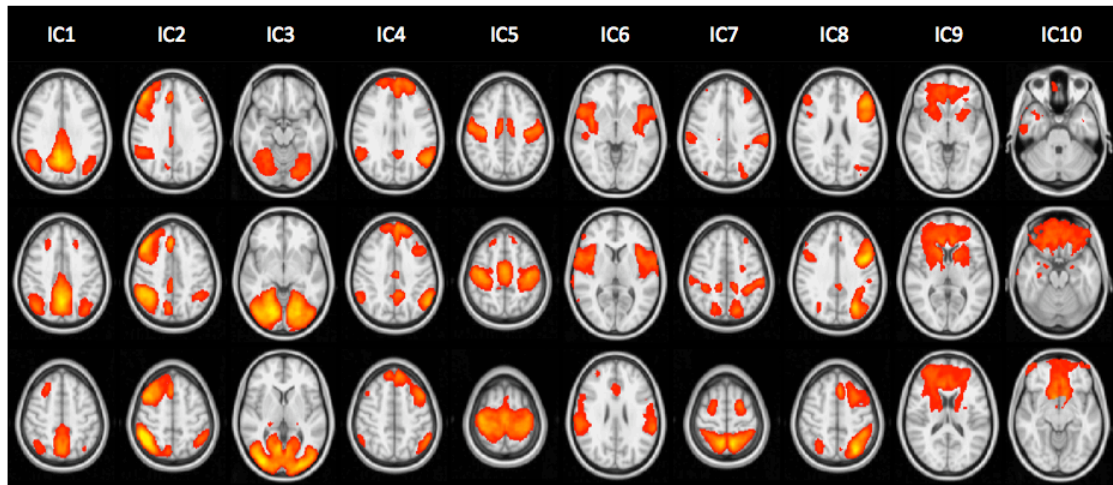


Fig. 5.2. Independent components (IC1-10) included in the analysis. Statistical images are shown in radiological convention with the right hemisphere displayed in the left.

5.4.3. Within-network connectivity

As seen in Fig. 5.3 and Table 5.1, lower OP (the correlation between subjective and objective action attribution) was associated with increased connectivity of IC10, a medial frontal network spatially (IC10, $r = .29$) and temporally (see Fig. 5.4) linked to the DMN, with a number of brain regions, including the paracingulate and anterior cingulate regions (peak voxel = MNI coordinate 4 44 -6, FWE corrected: $p = 0.026$), lateral occipital gyrus (peak voxel = MNI coordinate 50 -64 -2, FWE corrected: $p = 0.028$), and cerebellum (right VI). Though correction has not been applied in similar studies, as an indication of the strength of the effect, the peak voxel in the statistical image reached a corrected p-value of 0.18 when false discovery rate (FDR) correction for multiple (10) network comparisons was applied. Ambiguity-related misattribution was also associated with increased connectivity between IC10 and the cerebellum (left Crus II; peak voxel = MNI coordinate -30 -72 -40, FWE corrected: p

= 0.018) and reduced right inferior frontal gyrus (IFG) (homologue of Broca's area in the right hemisphere) connectivity with IC8, a left lateralised fronto-parietal network (peak voxel = MNI coordinate 52 28 -4, FWE corrected: $p = 0.03$, FDR correction for multiple (10) network comparisons, $p=0.16$).

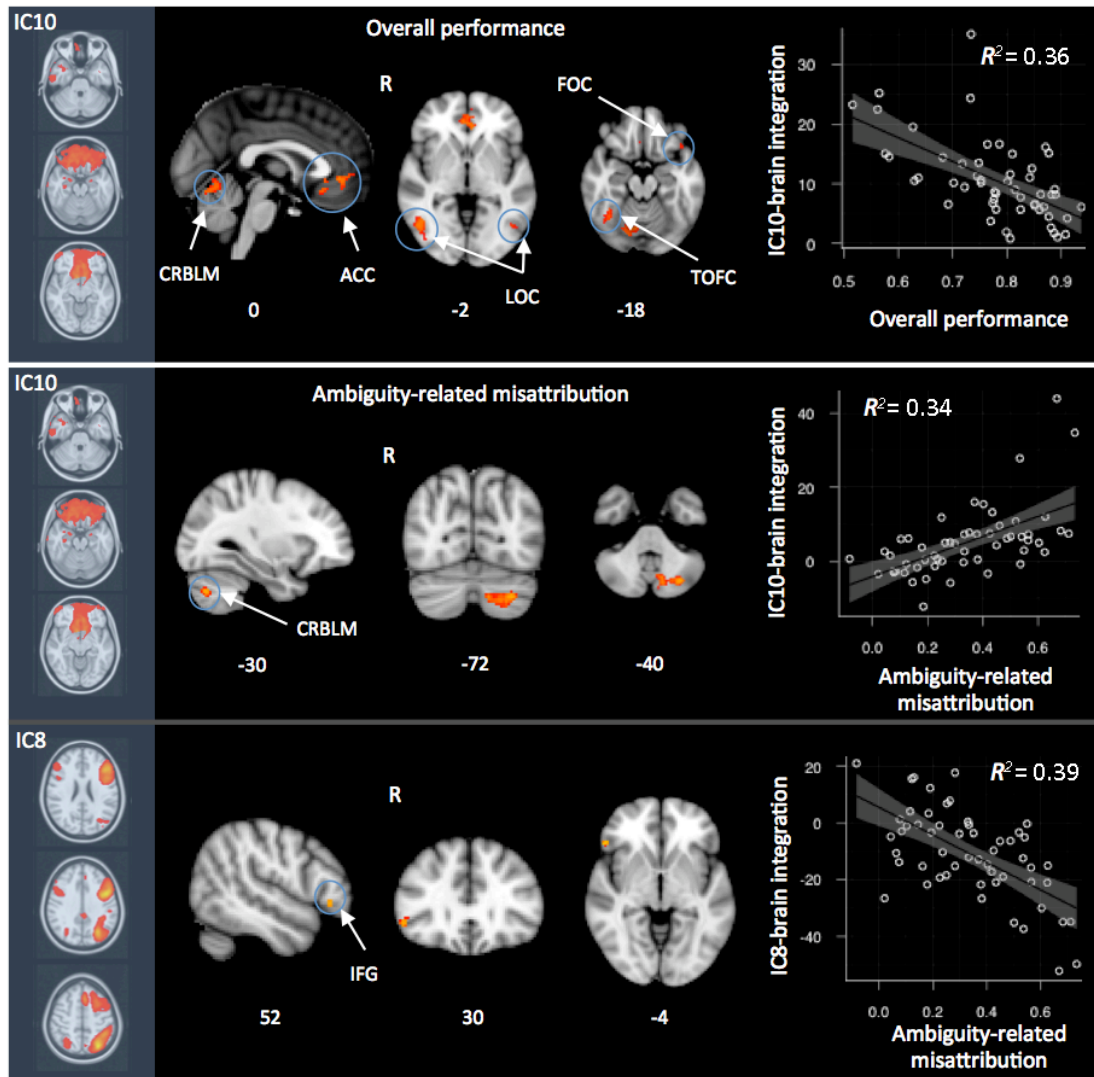


Fig. 5.3. Within-network connectivity. Task performance predicting brain regions with functional connectivity to IC10 (medial frontal network) (top panel); Ambiguity error predicting brain regions with functional connectivity to IC10 (medial frontal network) (middle panel) and IC8 (left fronto-parietal network). Corrected for multiple comparisons (grey matter voxels) using threshold-free cluster enhancement, shown at $P < 0.05$, corrected. The right side of images represents the left side of the brain. Scatterplots show the relationship between the behavioural variable (x-axis) and the degree of integration between the network and all significant voxels in the statistical image (y-axis).

Table 5.1. Within-network dual regression results. MNI coordinates for peak voxels are provided for each cluster with associated p-values corrected using threshold-free cluster enhancement. Values after each brain regions represents the associated cluster percentage. N = number of voxels; IC = independent component; BA = Brodmann area.

Network	Structures to which each cluster belongs to	Side	BA	N	P-value	MNI coordinates		
						X	y	z
IC10: reduced overall performance								
	Lateral Occipital Cortex, inferior division (12), Occipital Fusiform Gyrus (10)	R	37	705	0.028	50	-64	-2
	Paracingulate Gyrus (28), Cingulate Gyrus, anterior division (23), Subcallosal Cortex (24)	R	10	252	0.026	4	44	-6
	Lateral Occipital Cortex, inferior division (25), Inferior Temporal Gyrus, temporooccipital part (15)	L	37	89	0.036	-46	-60	0
	Right Crus II (69), Right Crus I (19)	R	n/a	47	0.036	24	-86	-36
	Lingual Gyrus (34)	R	18	10	0.043	14	-84	-12
	Frontal Orbital Cortex (55)	L	38	9	0.044	-42	22	-18
	Right VI (89)	R	n/a	8	0.048	28	-58	-30
	Right VI (81), Right V (19)	R	n/a	4	0.049	16	-60	-22
	Frontal Orbital Cortex (68)	L	38	3	0.048	-36	22	-8
	Temporal Occipital Fusiform Cortex (34)	L	19	3	0.047	-20	-58	-14
IC10: increased ambiguity-related misattribution								
	Left Crus II (44), Left VIIb (21)	L	n/a	257	0.018	-30	-72	-40
	Left Crus I (52), Left Crus II (33)	L	n/a	27	0.04	-10	-78	-32
IC8: reduced ambiguity-related misattribution								
	Inferior Frontal Gyrus (40), pars triangularis, Frontal Orbital Cortex (17)	R	38	11	0.032	52	28	-4

5.4.4. Between-network connectivity

Fig. 5.4 shows the correlation values of IC pairs. Squares below the diagonal line represent full correlation network comparisons, which allow for the influence of other ICs, while the partial correlations displayed above the diagonal line represent more direct measures of the relationship between IC pairs.

Using performance as predictor, the between-network comparison showed one significant difference for partial correlation values between IC9, corresponding to a frontal executive control network, and IC3, a visual network (Fig. 5.4, labeled OP; FWE corrected: $p = .019$). Higher OP during the agency task predicted significantly smaller correlation values between these two networks. No other differences emerged for full or partial correlation with performance as the predictor (FWE corrected: $p > .14$). Increased misattribution towards other in ambiguous conditions in the middle of the self-to-other continuum predicted increased full correlation between IC9 (the same frontal executive control network) and IC7, a dorsal attention network (Fig. 5.4, labeled AM, FWE corrected: $p = .035$). No other differences emerged for between-network comparisons (FWE corrected: $p > .9$).

IC9 implicated in both performance measures included subcortical regions and spatially correlated with the salience network ($r = 0.3$). Across participants, partial correlation comparisons showed that response fluctuation in this frontal network (IC9) correlated with IC6 (a temporal network) ($r = 0.84$) and IC4 (a DMN) ($r = 0.63$) and was negatively related to IC8 (a left-lateralised frontoparietal network) ($r = -0.42$). IC7, a dorsal attention network, was anti-correlated with IC4 (a DMN) ($r = -0.79$) and correlated with IC2 (a right-lateralised frontoparietal network) ($r = 0.9$) (see Fig. 5.4).

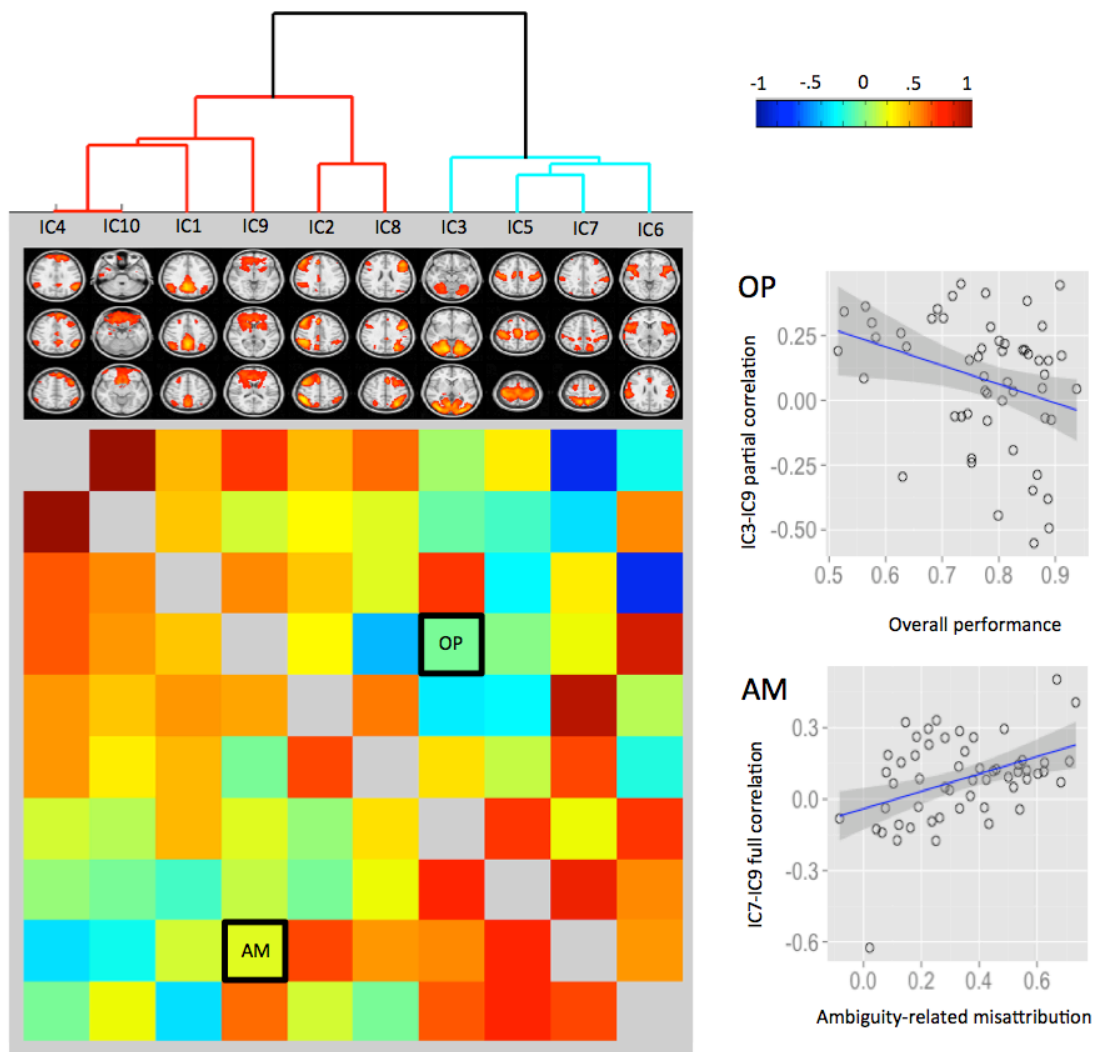


Fig. 5.4. Between-network connectivity (IC1-10). The right side of the images represents the left side of the brain. Full correlations across the cohort are shown below the diagonal line of the correlation matrix (left) with partial correlations shown above it. IC groupings on top of the matrix represent hierarchical clustering of IC timeseries. OP (overall performance) represents a significant decrease in partial correlations between IC3 (visual network) and IC9 (executive control network) (FWE corrected: $p = .019$). AM (ambiguity-related misattribution) represents a significant increase in full correlations between IC7 (visual/attention network) and IC9 (executive control network) (FWE corrected: $p = .035$). Corresponding scatterplots are shown on the right.

5.5. Discussion

Using resting state fMRI and an agency task, we investigated whether functional connectivity within and between networks during rest varies in relation to individual differences in agency task performance. Our findings indicate that lower overall performance and increased ambiguity-related misattribution was associated with increased connectivity between a medial prefrontal network (the anterior DMN) and other brain regions, including the anterior and paracingulate cortex, lateral-occipital gyrus, and the cerebellum. Ambiguity-related misattribution predicted reduced connectivity of a left lateralised frontoparietal network with the inferior frontal gyrus (Broca's area homologue in the right hemisphere). Connectivity (correlation) between a second more lateral prefrontal network and a visual and attention-related network was also related to lower performance.

5.5.1. Within-network functional connectivity and overall performance

The association between agency performance in our task and variation in a medial prefrontal network is consistent with studies that implicate this region in agency through its putative role in performance monitoring (reviewed in Van Noordt & Segalowitz, 2012). The medial prefrontal cortex (MPFC) has specifically been implicated in organising behaviour in the temporal domain (Fuster, 1997, 2001; reviewed in Vogeley & Kupke, 2007). This temporal association makes sense in the context of the task used here because participants' attribution judgments were based upon the temporal discrepancy between their actions and auditory outcome. Imaging studies also suggest that the MPFC is a key substrate for social cognition (Gallagher et al., 2000; Goel, 1995), integrating self-other information across time (reviewed in Van Overwalle, 2009). With reciprocal connections to brain areas associated with memory (hippocampus), emotion processing (amygdala) and higher-order information processing (DLPFC), this region is thought to play a regulatory role in goal-directed behaviour (reviewed in Wood, & Grafman, 2003).

As an anterior node of the DMN (Buckner, Andrews-Hanna & Schacter, 2008), the MPFC is thought to play an important role in maintaining the sense of self, showing particular sensitivity to self-referential processing, while posterior nodes (i.e., PCC; IPL) respond to stimuli relating to others (Northoff and Bermpohl, 2004; Molnar-

Szakacs & Uddin, 2013). For example, the MPFC has previously been associated with the retrieval of autobiographical memory (Svoboda et al., 2006), remembering self- versus externally-generated words (Vinogradov et al., 2008), self-referential episodes (Zysset et al., 2002) and self-knowledge (reviewed in Van Overwalle, 2009). It may be that agency performance is more determined by how regions associated with self are related to the rest of the brain than by regions associated with processing of other.

The DMN and its anterior node in particular has also received considerable interest in the study of neuropsychiatric conditions associated with agency dysfunction. For example, combined structural and functional imaging conducted by Pomarol-Clotet et al. (2010) revealed overlapping regions of abnormality in the MPFC in people with chronic schizophrenia compared to matched controls. Similarly, reduced task-related deactivation of the MPFC (Whitfield-Gabrieli et al., 2009; Pomarol-Clotet et al., 2008) and over-activation of this region during rest (Unschuld et al., 2014) has been associated with cognitive deficits related to schizophrenia. This pattern of findings is consistent with the direction of our results given the established link between positive schizotypy and reduced agency performance (Frith, 2005; Jeannerod, 2009).

In particular, this network expanded into neighbouring anterior cingulate regions previously associated with agency-relevant functions such as conflict monitoring, attention, decision-making, and emotional regulation (reviewed in Devinsky, Morrell & Vogt, 1995; Paus et al., 1998; Botvinick, Cohen & Carter, 2004). One model of the ACC proposes that it interacts with other prefrontal regions, combining executive processes with representations of emotional states to enable appropriate behavioural responses to events relevant to self (Paus, 2001). Interestingly, anterior cingulate regions are also amongst those that have been consistently implicated in hallucination-related phenomena (reviewed in Allen et al., 2008; Fornito et al., 2009). Notable examples include relationships found between psychosis proneness and over-activation in the ACC during self-reflection (Modinos et al., 2011), and between the morphology of the paracingulate sulcus and hallucinatory experiences (Garrison et al., 2015).

In our findings prefrontal connectivity with a lateral occipital, inferior temporal region and the cerebellum also increased in association with lower overall performance. The former includes the “extrastriate body area” (EBA) – a region often implicated in agency tasks with particular sensitivity to externally-generated stimuli (David et al., 2007; 2008; reviewed in Jeannerod, 2004), in addition to its association with embodiment (Arzy et al., 2005). This region is also just posterior to the inferior parietal lobe also shown to be sensitive to action-outcome discrepancy that characterises externally-caused events and found to be overactive during agency tasks in patients with positive symptoms of schizophrenia (e.g., Farrer et al., 2004; Spence et al., 1997).

Similarly, regions of the cerebellum have been associated with other-agency and action feedback discrepancy (Blakemore et al., 2001). Though still little is known about the fronto-cerebellar pathway, it has been suggested that it may facilitate functions that are implicated in agency processing such as the transfer of sensorimotor information and motor prediction and learning (Watson et al., 2015; Kalmbach et al., 2009). Compared with healthy controls, first-episode schizophrenia patients show increased resting state connectivity between DMN and the cerebellum (right Crus II) (Guo et al., 2015).

More generally, it makes sense that connectivity between regions associated with self (MPFC) and those associated with other increased with lower performance. This suggests that self-other differentiation depends on regions associated with self and other being functionally distinct from one another. This rationale is in line with findings of overlap between the self and non-self cortical maps in individual with positive symptoms of schizophrenia (Jardri et al., 2011).

5.5.2. Within-network functional connectivity and ambiguity-related misattribution

Confirming previous behavioural findings (de Bezenac et al., 2015), ambiguity-related misattribution was biased towards other, suggesting a tendency to experience self-generated events as belonging to other in ambiguous situations where the likelihood of self and other-generated tones was equal. The extent of this bias also implicated the medial frontal network, specifically predicting increased connectivity with the cerebellum (Left Crus II). More specific examination of functional fronto-

cerebellar pathways may therefore contribute to a clearer understanding of the role that the cerebellum plays in agency and in social cognition more generally (Van Overwalle et al., 2014).

The only regions that showed increased network connectivity in relation to better performance and, more specifically, reduced ambiguity-related misattribution towards other was an area in the IFG that corresponded to the right homologue to Broca's area. Activity in this region has been shown to be responsive to self-specific stimuli (Uddin et al., 2005; Kaplan et al., 2008; Qin & Northoff, 2011) and has been implicated in the experience of auditory verbal hallucinations (Sommer et al., 2008). In our findings, reduced ambiguity-related bias was associated with increased connectivity between this region and the left lateralised frontoparietal network that includes Broca's area. Using dynamic causal modelling, Ćurčić-Blake et al. (2013) found reduction in connectivity between Broca's area and its right homologue in patients with hallucinations. Furthermore, reduced connectivity between the latter and the left temporoparietal junction (TPJ), part of the left frontoparietal network has also been associated with hallucinations (Vercammen et al., 2010). It may be that cross-hemisphere co-activation of these regions reduces the likelihood of experiencing self-generated action and thoughts as originating from an external source. This could be tested experimentally by using neuro-stimulation techniques to modulate functional relationships between aforementioned regions during an agency task or with patients experiencing hallucinations (Moseley, Fernyhough, & Ellison, 2013).

5.5.3. Between-network functional connectivity

Examining connectivity between networks, both agency performance measures were associated with the more lateral, executive control prefrontal network (Smith et al., 2009; for reviews see Botvinick et al. 2004; Dosenbach et al. 2007). This network spatially overlapped with the salience network and included subcortical regions and response fluctuations correlated with a temporal and default mode network. That agency performance modulated a frontal network commonly engaged by tasks requiring executive control is not surprising given the high-level functions likely to be involved in self-other processing. Such prefrontal regions are thought to regulate the flow of ongoing processing via dopaminergic neurotransmitters, particularly

affecting systems responsible for perception, action selection, and emotional evaluation (Miller & Cohen, 2001).

Our findings show that correlation between this frontal network and a visual network increased as overall agency performance decreased. While it is not immediately apparent why a visual network was implicated in agency performance, it suggests that autonomy between prefrontal and perceptual brain areas during resting state has important implications for accurate agentic decision-making.

Ambiguity-related misattribution increased with correlation between the same frontal network and a dorsal attention network with fluctuations highly correlated with a right-lateralised frontoparietal network and anticorrelated with a DMN across participants. While further hypothesis-driven research is required, our pattern of results suggests that individuals who have a tendency to experience their actions as belonging to others in the absence of clear information for self-other differentiation may be hyper-attentive/vigilant during rest, a trait previously observed in people with schizophrenia (Mar, Smith & Sarter 1996). Given the previous link between ambiguity processing and hallucination proneness (de Bezenac et al., 2015), this finding indirectly supports evidence implicating the deregulation of task-positive and task-negative networks in schizophrenia (Wotruba et al., 2013; Nygård et al., 2012). However, ambiguity-related misattribution was only a significant predictor in the full-correlation comparison, suggesting that the effect may be modulated by another network. Hypotheses-driven mediation models could be used in future work to uncover indirect relationships.

5.5.4. General

With the exception of the finding relating agency performance to left frontoparietal connectivity with the right IFG, connectivity within and between networks was related to lower performance (including increased ambiguity-related misattribution). This is in line with studies that associate neural inhibition, particularly of the DMN, to task difficulty and performance accuracy (Harrison et al., 2011; Gilbert et al., 2012; Polli et al., 2005; Engström, Landtblom, & Karlsson, 2013), as well as those showing general over-activation and connectivity to be associated with schizophrenia (Whitfield-Gabrieli et al., 2009; Peeters et al., 2015; Shim et al., 2010; Yang et al.,

2014). For example, Driesen et al. (2013) found that schizophrenia-like symptoms induced through ketamine were associated with increased global functional connectivity between networks that are normally functionally independent during resting-state fMRI. This hyperconnectivity seems to specifically implicate prefrontal areas (Vollenweider et al., 1997; Whitfield-Gabrieli et al., 2009; Anticevic et al., 2015). Our findings, showing that two prefrontal networks were modulated by agency performance suggests a specific role for the prefrontal cortex and its functional connections with other parts of the brain in self-other processing. An over-connected prefrontal lobe could mediate distorted boundaries between self and others and lead to lower attribution performance. Given the correlation between fluctuation in the medial frontal network and the DMN, our findings partially support theoretically-driven predictions implicating the DMN in self-other differentiation (Robinson, Wagner & Northoff, 2015).

Finally, that cerebellar, frontal and parietal structures known to be involved in temporal processing (Coull, Davranche, Nazarian, & Vidal, 2013) were implicated in agency performance suggests that timing is an important cue for self-other differentiation and that there may be significant overlap between temporal discrimination and agency performance. This is in line with findings associating reduced performance on both timing and agency tasks to increased psychopathology (Papageorgiou et al., 2013; Carroll et al., 2008; Spence et al., 1997; Frith, 2005). Disentangling, and assessing the overlap between inter-individual variation in temporal/spatial discrimination and agency performance in relation to neural response in future work could further our understanding of agency-processing.

5.6. Conclusion

Using a data-driven approach, we present initial evidence for the relevance of the anterior brain's resting state activity in agency processing. Increased connectivity of the prefrontal cortex with other parts of the brain related to a diminished ability to distinguish self from other-generated events. More specifically, lower performance predicted increased connectivity between medial prefrontal regions associated with self-referential processing and regions shown to be sensitive to externally-generated stimuli. On the basis of these findings we contend that a greater understanding of

agency-related patterns of functional connectivity during rest has potential to contribute to theories of self-other representation in the brain and, importantly, to enhance our understanding of conditions, like psychosis, where such representations are challenged.

5.7. Acknowledgements

The authors would like to acknowledge the Institute of Psychology Health and Society, University of Liverpool for funding data collection and a studentship. We thank Fahad Alhazmi and Joe Furlong for their assistance with data collection.

5.8. References

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CHAPTER 6

General discussion and conclusions

6.1. Purpose and rationale of the study

This doctoral research examined behavioural and neural underpinnings of self-other differentiation with a particular focus on response to ambiguous situations where information for distinguishing between events caused by self and other is reduced. The study began by defining the concept of ambiguity, putting forward the idea that it plays a key role in the developing sense of self and in learning to differentiate self from other, both as a physical entity and agent with influence on surroundings. The proposal was that experience in contexts that require self-other differentiation yet which makes such differentiation challenging may provide optimal conditions for developing reality-testing skills necessary for self-other processing. With attunement in early caregiver-infant interactions framed as one such context, the argument positioned vulnerability to psychosis within a developmental framework. However, it was also noted that attribution abilities negatively related to associated phenomena in previous research (Frith, 2005; Bentall et al., 2007; Jeannerod, 2009), may be malleable and improve through experience/practice. Using joint action and, more specifically, music-making as a case in point, it was argued that behaviours that put the sense of self into question – often by introducing a high degree of coherence between autonomous agents – may be understood as having the functional role of maintaining a coherent sense of self throughout life by refining reality-testing reflexes relating to self-other boundaries. As such, the first chapter concluded by proposing that increased insight into the role of ambiguity may enhance our understanding of mechanisms underlying ‘self-disorders’ such as schizophrenia and may eventually extend the range of social and arts-based therapeutic possibilities. Despite the scope of such proposals and their wide-ranging implications for mental health, initial predictions were put forward for testing in the context of the experimental investigations presented in Chapters 2-5.

Below is a summary of these experimental findings with a brief discussion about how these relate to the above theoretical ideas, general limitations and directions for further investigation. More specific associations between the findings of each study and previous behavioural and neuroimaging work are included in the discussion sections of experimental study write-ups (i.e., sections 2.5, 3.5, 4.5 and 5.5).

6.2. Summary of experimental findings

The aim of the first experimental study (Chapter 2) was to develop a novel task that would allow the amount of control that self has compared to other over action-outcomes to be systematically manipulated. In so doing it addressed methodological challenges identified in previous agency paradigms (see section 2.2). This was achieved by modulating the probability that auditory tones would result from finger taps belonging either to self or to other. In contrast to previous examinations of agency that distorted self-generated feedback and used error to subjectively determine the point of greatest uncertainty for each individual, the approach used here allowed ambiguity to be objectively defined as conditions where the likelihood for self- and other-generated outcomes was equal.

Misattribution, calculated as the difference between subjective locus of control and the actual proportion of control that a participant possessed, was examined along the self-to-other continuum in a multilevel analysis using hallucination proneness and musical experience as second-level predictors. In contrast to hallucination proneness (which has previously been linked with increased misattribution), musical experience was predicted to be associated with reduced attribution errors: the underlying supposition was that engaging in behaviours requiring self-other differentiation, on the one hand, yet which also render this task challenging, on the other, can make individuals better at monitoring self in relation to sensory outcome belonging to other/s. Furthermore, given that musical skill is not ‘innate’ but learnt through experience (or thousands of hours of practice), examining musical experience in relation to attribution abilities was used to provide preliminary insight into the malleability of this competence.

Findings from 40 participants revealed that misattribution peaked in the middle of self-to-other continuum where ambiguity was greatest. Misattribution tended to be biased towards other in ambiguous conditions for all participants in the sense that individuals were more likely to experience tones as having been externally rather than self-generated. As hypothesised, this pattern of results was related to higher hallucination-proneness and contrasted to the pattern of reduced ambiguity-related misattribution associated with musical experience. These findings not only provided initial support for the idea that causal ambiguity plays a key role in self-other processing, but also that action attribution abilities are malleable and may improve with experience in contexts that blur the boundaries between self and other.

The aim of the second experimental study (Chapter 3) was to conduct an initial examination into neural response to ambiguity in the attribution task outlined above using a parametric fMRI block-design paradigm. The implementation of linear and non-linear stimulus-response functions allowed differentiation between neural activity related to control belonging to self (negative linear), other (positive linear) and ambiguity-related response (positive/negative quadratic). Confirming findings from the previous study (Chapter 2), ambiguity-related misattribution was observed. Testing stimulus-response functions in task-sensitive brain regions, revealed a general negative trend of BOLD response in relation to the self-to-other manipulation, indicating sensitivity to control belonging to self. However, all anatomically defined regions also displayed significant non-linearity with decreased response in ambiguous conditions compared to the extremes of the self-to-other continuum (see Table 3.5). This provided new insights into agency-related ambiguity-processing in the brain, suggesting that causal relationships are processed in terms of their distinctiveness from uncertain contexts.

Task performance accentuated this U-shaped quadratic pattern in the precentral gyrus and a number of subcortical regions, including the putamen, caudate, and amygdala. Another important finding from this study was that individuals who made more errors (misattribution biased towards other) across the entire task showed increased response in regions associated with the DMN. This provides initial evidence of how individual differences can modulate neural response during self-other processing. As argued in sections 3.5 and 4.5.2, the observed response direction fits with evidence

associating expert performance with the deactivation of DMN regions (Harrison et al., 2011; Gilbert et al., 2012; Polli et al., 2005; Brewer et al., 2013; Sperduti et al., 2012), as well as clinical findings associating altered neural function of these regions to positive symptoms of schizophrenia (reviewed in Adams & David, 2007).

Given individual-difference findings related to ambiguity in the behavioural study (Chapter 2) and the performance-related response modulation observed in the fMRI investigation (Chapter 3), a more in-depth examination into how such differences modulate neural response during the attribution task was conducted in Chapter 4. Again reflecting the previous behavioural and imaging results, it was only in ambiguous conditions that neural response was found to vary between individuals. Increased response in a number of brain regions and networks was associated with positive, but not negative, schizotypy (measured using O-LIFE sub-factors) and an inability to tolerate ambiguity. These included the ACC and in a number of networks, including the DMN, visual, auditory and sensorimotor and regions (i.e., cingulate and temporal), previously implicated in hallucination, agency and ambiguity-processing. In contrast, reduced response in the same areas was associated with increased musical experience and improved task performance. In addition to the data-driven task-based ICA, a whole brain univariate analysis showed increased activation while processing the most ambiguous stimuli in cingulate and temporal regions previously associated with both hallucination (reviewed by Allen et al. 2008) and ambiguity-processing (e.g., Botvinick et al., 2001) (for more detail see sections: 4.2.2., 4.2.4., and 4.5).

The purpose of the fourth empirical study (Chapter 5) was to examine the effects of attribution performance, including performance specifically related to ambiguity, on resting-state functional connectivity. Using ICA, dual regression and network analyses, the study investigated brain-behaviour relationships both within and between large-scale networks. In line with region-specific response decreases observed in studies 2 and 3 associated with individual differences such as task performance and schizotypy, a medial prefrontal network (the anterior node of the DMN) showed increased connectivity with the anterior cingulate, temporo-occipital and cerebellar regions in individuals with lower overall performance on the attribution task (completed outside the scanner). Increased frontoparietal

connectivity with the right inferior frontal gyrus was the only pattern associated with better task performance. That overall and agency performance was found to predict spontaneous fluctuations of neural response even when participants were not explicitly engaged in an agency task, suggests that the ability to distinguish self from other may be linked to neural function and an important distinguishing feature between individuals. More specifically, it implicates the relationship between the prefrontal cortex and the rest of the brain in this process.

6.3. Implications of the study and future directions

6.3.1. Implications of empirical findings

Findings presented in this thesis provide initial support for the conceptual framework outlined in Chapter 1 regarding the putative role that ambiguity plays in self-other processing and in the experience of self-other action attribution. Behavioural and physiological indicators from all four empirical studies suggest that it is in contexts that lack information about whether the outcome of behaviour belongs to self or other that individuals show the greatest performance and neural disparities. While large inter-individual variability in agency performances is often observed (e.g., Farrer et al., 2004), few studies directly investigate the source of this variability. Thus, the present work constitutes an important step forward in filling this gap. Results not only confirm the previously established link between positive schizotypy and misattribution (e.g., Jeannerod, 2009; Frith, 2005; Bentall et al., 2007), but also provide credence to the idea that psychosis-related deficiencies may be more specifically associated with difficulties or lack of experience in dealing with contexts characterised by reduced agency information (de Bezenac et al., 2015). This idea requires further testing in research involving clinical samples. Empirical studies also point towards attribution abilities as being malleable, improving through experience in ambiguous contexts – a proposition that may have clinical implications.

The imaging results presented here shed additional light on the neural mechanisms of agency and allow further, more specific predictions to be formulated for future studies investigating ambiguity in self-other action attribution. For example, in accordance with research linking deactivation with functional efficiency (Mckiernan

et al., 2003; Pomarol-Clotet et al., 2008), reduced ambiguity-related response was consistently associated with higher performance in the three fMRI investigations. In accordance with previous work on self-other processing (discussed in sections 3.5, 4.5, and 5.5) findings implicated medial prefrontal regions (anterior DMN) and its relationship with the rest of the brain in the ability to accurately attribute actions to self and to other, allowing the direction of response within and between specific brain regions to be specifically tested in future investigations. The behavioural or experiential effect of dampening response or connectivity in regions positively associated with schizotypy and reduced task performance (e.g., using non-invasive brain stimulation such as rTMS or tDCS), for example, could also be investigated to determine the contribution of implicated brain regions to self-other processing. The network approach taken in Chapters 4 and 5 also builds on previous agency work, given the lack of network-based neural accounts of agency and the increasing evidence that large-scale networks functional integration measures can constitute a more accurate fingerprint of cognitive phenomena than other approaches (e.g., Bressler & Menon, 2010).

6.3.2. Theoretical implications

Drawing from perceptual and developmental psychology and from previous agency research (e.g., Gibson 1979; Bregman, 1994; Stern 1985; Fonagy et al., 2004; Farrer et al., 2004; David et al., 2008), the conceptual framework laid out in Chapter 1 has the potential to contribute to existing models of agency by placing dynamic features of experience at the centre. For example, the comparator model focuses on the relationship between sensorimotor predictions and action outcomes (Wolpert & Miall, 1996; Frith, Blakemore, & Wolpert, 2000). By describing how such internal and external signals can vary in multiple ways including intensity, timing, and form – informed by the work of Daniel Stern (1985) – the framework provides a vocabulary that can lead to a more developed model of this relationship.

Furthermore, Chapter 1 makes reference to internally derived signals other than sensorimotor prediction. For instance, affective sensations can also be more or less coherent with signals resulting from action-outcomes and are likely to play an important role in determining feelings of agency. This enables less investigated parameters particularly relevant to agency-related disorders to be considered within

the same theoretical frame and inform the development of new experimental paradigms. For example, the neutral agency task developed as part of this study could be adapted to include an emotional dimension in future research. More specifically, the effects of positively and negatively valenced stimuli could be examined in situations of reduced information for self-other differentiation. Indicators of modulating internal arousal, such as heart rate variability, electrodermal activity and body temperature, could also be compared to external stimuli (auditory, visual, or tactile) to examine the effects of coherence between internal and external signals on perceived agency.

In contrast to considering agency as occurring within discrete moments that either belong to self or to other, the proposed framework emphasises that coherence of sensory signals from inside and outside the body varies continuously over time and at different timescales (e.g., sensorimotor processing or the general control that a person feels over their life - Gallagher, 2013). In accordance with recent conceptual shifts in cognitive science (Gallagher, 2013; Engel, Friston, & Kragic, 2016; Marsh et al., 2009; Stern, 2000), a more situated stance that implicitly examines experience as unfolding in time has the potential to bring together aspects of agency that have traditionally been addressed in non-overlapping research domains (e.g., sensorimotor agency and attribution theory). The task used in the experimental studies is a step in this direction given that, in contrast to previous agency paradigms, control can more naturalistically shift between belonging to self and other within trials. Attribution is continuous and can be ambiguous because it is based on weighing up stimuli belonging to both self and other picked up over a period of time (10-12 seconds in the case of this task).

While mental health difficulties associated with the perception of self are viewed within a developmental framework and the importance of early caregiver-infant interaction is recognised, the model also leaves open the possibility for continued life-long development by proposing that the sense of self and the ability to distinguish self from other is malleable. A route through which such development may take place is specified. The functional description of ambiguity, as increased signal coherence between but not within entities, points towards practical ways of

measuring and manipulating the degree of ambiguity that exists in both controlled and more naturalistic settings.

More generally, the ideas laid out in Chapter 1 are consistent with neuro- and cognitive-developmental accounts of psychosis proneness as well as with long-standing non-medical therapies. Parallels are drawn between socio-affective interactions in early infancy that play an important role in the developing sense of self and the experience of coordinating behaviour with others through music-making. The two experiences have a number of commonalities, not least that both can be intuitively grasped without the need for verbal thinking or communication and involve the “flow of forms in time” (Stern, 2000). This comparison allows cultural and artistic practices to be understood as having a functional role in maintaining mental wellness. In accordance with approaches that reject the bio-medicalisation of mental illness (e.g., Bentall, 2004; Deacon, 2013; Watters, 2011), this reinforces the idea that psychological disorders can only be fully addressed in relation to the social, political and cultural contexts that sustain or maintain them. Rather than being predetermined by an individual’s particular genetic/neurological makeup or by the behaviour of family members including caregivers, mental illness is more fundamentally seen as causally related to processes of power that allow contexts and practices that have evolved to promote mental wellness to be eroded (Dewey, 1934; Reed, 1996; Blacking, 1974). However, an evidence-based awareness of the psychological outcomes that emerge from the interplay that exists between individuals and their surroundings is a necessary step towards genuine solutions to psychological difficulty. This project aims to contribute to such an endeavour by providing a framework for thinking about and testing aspects of this interplay involving individual differences associated with the perception of boundaries between self and other. As such, it speaks to concepts that consider individual differences in the quality of interpersonal relationships such as attachment theory (Bowlby, 2005), providing possible explanations for how such differences emerge and the degree to which experience-driven development is possible throughout life.

6.3.3. Applied directions with clinical implications

The potential of being able to effectively manipulate/maximise ambiguity is not limited to the validation of theoretical ideas, but extends to developing practical ways of improving self-other monitoring capabilities. With the definition of ambiguity outlined in Chapter 1 in mind, a useful starting point is to observe and analyse behaviours across multiple domains that go against invariants, i.e., that increase coherence between and incoherence within entities across sensory modalities, to identify the most effective ambiguity-promoting methods.

Given that behaviours including music-making, dance and certain sports require years of intensive training often from early childhood, an important step will be to design environments capable of amplifying ambiguity for participants without the trained motor and coordination skills. For example, this could be achieved through computer-mediated interaction between individuals and, more specifically, virtual or augmented reality settings that manipulate the correlation between sensory feedback belonging to self and other in ways that promote ambiguity (i.e., introducing incoherence within and coherence between self- and other-generated feedback). Such environments could also be dynamic: optimised for specific participants by using performance and physiological measures collected and analysed in real-time to adjust the degree of challenge that participants experience. A flexible, participant-sensitive setup of this sort would also protect against intervention-related distress in relevant user groups.

Though the effect of improving self-other monitoring abilities on the experience of unsolicited and distressing misattributions associated with psychosis is still an open question, a setup that accelerates and makes such an improvement accessible has the potential to function as a sensorimotoric therapeutic intervention. As noted in Chapter 1, few treatments target lower order configurations of self that involve more primitive sensations of one's body as a coherent entity or agent related to other individuals. This possibility is supported by evidence for the therapeutic benefits of behaviour described here as ambiguous such as music-making (e.g., Silverman, 2003; Peng et al., 2010; Na & Yang, 2009; Kantrowitz et al., 2013). However, the identification of ambiguity as an underlying feature that drives such benefits makes it

possible to design environments that amplify the possibility of positive clinical change.

6.4. General limitations

A potential limitation of the experimental research is that the study explored brain-behaviour relationships in a non-clinical sample. However, it is widely acknowledged that dimensional measures of schizotypy are a useful first step to examining underlying mechanisms of psychosis, with the advantage of avoiding confounding effects associated with medication or long-term chronic illness (Raine, 2006). Examining self-other ambiguity-processing by comparing clinical and non-clinical populations informed by the behavioural and neural hypotheses generated by this study would be the logical next step in further testing the clinically-related propositions put forward in Chapter 1.

Given the scope of the proposed framework, many aspects of which had not been explored in previous imaging studies as well as the novelty of the behavioural task employed, the testing of narrowly defined hypotheses relating to neural function was premature in the context of studies included here. While this necessarily limits the definitive conclusions that can be drawn from the study, it also allows for a flexible and iterative approach towards the subject matter – one that progressively leads to more circumscribed hypotheses excluding other interpretations. The imaging analysis approach taken here can be very useful for the initial exploration of patterns of activity across novel conditions particularly in light of advancements in whole-brain error control methods (Poldrack, 2007). It also avoids the pitfalls associated with more constrained ROI choice biases in the absence of previous imaging work and evidence specifically related to the subject matter.

Similarly, due to the correlational nature of aspects of the data, we must be cautious of interpreting findings in explanatory causal ways. For example, it is not possible to conclude that findings relating to musical experience demonstrate the plasticity of attribution skills through experience in ambiguous settings. All we can say is that the data and findings are though consistent with this being the case. Strengthening the

evidence presented here will require experimental setups that compare attribution performance effects following interventions that either maximise or minimise ambiguity. Furthermore, to determine the extent to which this idea can generalise from music-making to other activities, as suggested in Chapter 2, experiments will need to tap into multisensory, ambiguity-promoting strategies found in joint-behaviours other than music. The finding of the present research provides a starting point for assessing and monitoring the behavioural and neural effect of such a procedure over time. For example, reduced misattribution coupled with a reduction of brain connectivity with the anterior DMN could indicate a positive effect that can be examined alongside clinical changes such as the quantity and quality of psychotic experiences during, and following an ambiguity-promoting intervention.

6.5. Summary and conclusions

In conclusion, despite the manifold questions that remain, the behavioural and neuroimaging findings of this research provide initial support for the proposed role of ambiguity in agency and lead to further testable hypotheses. The study not only confirms the link between action attribution deficiencies and positive schizotypal traits, but also suggests that such deficiencies may be related to difficulties in processing ambiguity between action outcomes belonging to self or other. Data showing musical experience to be associated with reduced misattribution and associated neural correlations of task performance within ambiguous conditions leaves open the possibility that action attribution style is malleable, and that extensive experience in intricate joint-action could improve self-other processing abilities. The present work more specifically constitutes a step towards understanding the source of between-individual variability observed in agency performance. The relevant clinical question of whether experience-based improvement in action attribution can lead to a reduction of hallucinations and delusions is a worthwhile avenue for future investigation. However more insight into behavioural and neural responses to ambiguity is also required. Developing this research may extend the range of therapeutic interventions, for example, through the design of maximally ambiguous environments that can be titrated by individuals to maintain benefit while controlling feelings of distress. Given that the aetiology of

various mental disorders may be viewed as the mind misinterpreting its own experience of itself and of other (Fonagy & Campbell, 2015), the praxis of self-other ambiguity has the potential to contribute to a more refined understanding of the interconnections that exist between mental health difficulties and, more importantly, an awareness of the contexts that promote mental wellness throughout life.

6.6. References

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APPENDIX A

Revised Launay Slade Hallucination Scale (LSHS-R)

Waters, F. A., Badcock, J. C., & Maybery, M. T. (2003). Revision of the factor structure of the Launay–Slade Hallucination Scale (LSHS-R). *Personality and Individual Differences*, 35(6), 1351-1357.

This questionnaire is concerned with certain experiences you might have had in your life. Please rate each question using the scale:

- 0 = Certainly does not apply
- 1 = Possibly does not apply
- 2 = Unsure
- 3 = Possibly applies
- 4 = Certainly applies

1. No matter how hard I try to concentrate, unrelated thoughts always creep into my mind

0 1 2 3 4

2. In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it

0 1 2 3 4

3. Sometimes my thoughts seem as real as actual events in my life

0 1 2 3 4

4. Sometimes a passing thought will seem so real that it frightens me

0 1 2 3 4

5. The sounds I hear in my daydreams are generally clear and distinct

0 1 2 3 4

6. The people in my daydreams seem so true to life that sometimes I think they are

0 1 2 3 4

7. I often hear a voice speaking my thoughts aloud

0 1 2 3 4

8. In the past, I have had the experience of hearing a person's voice and then found that no-one was there

0 1 2 3 4

9. On occasions, I have seen a person's face in front of me when no-one was in fact there

0 1 2 3 4

10. I have heard the voice of the Devil

0 1 2 3 4

11. In the past, I have heard the voice of God speaking to me

0 1 2 3 4

12. I have been troubled by hearing voices in my head

0 1 2 3 4

APPENDIX B

Tolerance of Ambiguity Scale (ToA)

Original source: Budner, S. (1962). Intolerance of ambiguity as a personality variable. *Journal of personality*.

Please respond to the following statements by indicating the extent to which you agree or disagree with them. Fill in the blanks with the number from the rating scale that best represents your evaluation of the item.

Rating Scale

- 1 Strongly disagree
- 2 Moderately disagree
- 3 Slightly disagree
- 4 Neither agree nor disagree
- 5 Slightly agree
- 6 Moderately agree
- 7 Strongly agree

- 1. ____ An expert who doesn't come up with a definite answer probably doesn't know much
- 2. ____ I would like to live in a foreign country for a while
- 3. ____ There is really no such thing as a problem that can't be solved.
- 4. ____ People who fit their lives to a schedule probably miss most of the joy of living
- 5. ____ A good job is one where what is to be done and how it is to be done are always clear
- 6. ____ It is more fun to tackle a complicated problem than to solve a simple one
- 7. ____ In the long run it is possible to get more done by tackling small, simple problems rather than large and complicated ones
- 8. ____ Often the most interesting and stimulating people are those who don't mind being different and original
- 9. ____ What we are used to is always preferable to what is unfamiliar.
- 10. ____ People who insist upon a yes or no answer just don't know how complicated things really are.
- 11. ____ A person who leads an even, regular life in which few surprises or unexpected happenings arise really has a lot to be grateful for.
- 12. ____ Many of our most important decisions are based upon insufficient information.
- 13. ____ I like parties where I know most of the people more than ones where all or most of the people are complete strangers.
- 14. ____ Teachers and supervisors who hand out vague assignments give one a chance to show initiative and originality
- 15. ____ The sooner we all acquire similar values and ideals the better
- 16. ____ A good teacher is one who makes you wonder about your way of looking at things

Scoring Key

Having intolerance for ambiguity means that an individual tends to perceive situations as threatening rather than promising. Lack of information or uncertainty, for example, would make such a person uncomfortable. Ambiguity arises from three main sources: novelty, complexity and insolubility. These three subscales exist within this instrument.

High scores indicate a greater INTOLERANCE of ambiguity. To score the instrument, the even numbered items must be reverse-scored. That is, the 7s become 1s; 6s become 2s etc. After reversing the even-numbered items, sum the scores for all 16 items to get your total score.

The 3 subscales also can be computed to reveal the major source of intolerance of ambiguity. Here are the items associated with each subscale.

Item	Subscale	Item	Subscale	Item	Subscale	Item	Subscale
1	I	5	C	9	N	13	N
2	N	6	C	10	C	14	C
3	I	7	C	11	N	15	C
4	C	8	C	12	I	16	C

(N) Novelty Score (2,9,11,13) _____

(C) Complexity Score (4,5,6,7,8,10,14,15,16) _____

(I) Insolubility Score (1, 3, 12) _____

TOTAL SCORE _____

Novelty indicates the extent to which you are (in)tolerant of new, unfamiliar information or situations.

Complexity score indicates the extent to which you are (in)tolerant of multiple, distinctive or unrelated information.

Insolubility indicates the extent to which you are in(tolerant) of problems that are very difficult to solve because, for example, alternative solutions are not evident, information is not available, or the problem components seem unrelated to each other.

Remember, the higher the score(s) the more intolerant of ambiguity you scored.

APPENDIX C

Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)

Mason, O., Linney, Y., & Claridge, G. (2005). Short scales for measuring schizotypy. *Schizophrenia research*, 78(2), 293-296.

1= Yes; 0= No

1. Do you stop to think things over before doing anything?
2. Can some people make you aware of them just by thinking about you?
3. Does a passing thought ever seem so real it frightens you?
4. Are you a person whose mood goes up and down easily?
5. Do you find the bright lights of a city exciting to look at?
6. Would you like other people to be afraid of you?
7. Are you usually in an average kind of mood, not too high and not too low?
8. Do you often overindulge in alcohol or food?
9. Does your sense of smell sometimes become unusually strong?
10. Do you frequently have difficulty in starting to do things?
11. When in the dark do you often see shapes and forms even though there is nothing there?
12. Do you feel that your accidents are caused by mysterious forces?
13. Are your thoughts sometimes so strong that you can almost hear them?
14. Do you often feel like doing the opposite of what other people suggest even though you know they are right?
15. Do you find it difficult to keep interested in the same thing for a long time?
16. Do you love having your back massaged?
17. Are you much too independent to get involved with other people?
18. Do you often feel the impulse to spend money which you know you can't afford?
19. Do you prefer watching television to going out with people?
20. Do you like mixing with people?
21. Is it hard for you to make decisions?
22. Do you ever have a sense of vague danger or sudden dread for reasons that you do not understand?
23. Have you ever felt the urge to injure yourself?
24. Are you easily distracted when you read or talk to someone?
25. Has dancing or the idea of it always seemed dull to you?
26. Is trying new foods something you have always enjoyed?
27. When in a crowded room, do you often have difficulty in following a conversation?
28. Do you consider yourself to be pretty much an average sort of person?
29. Are you easily distracted from work by daydreams?
30. Are you easily confused if too much happens at the same time?
31. Do ideas and insights sometimes come to you so fast that you cannot express them all?
32. Have you often felt uncomfortable when your friends touch you?
33. Do you think that you could learn to read other's minds if you wanted to?
34. Do you at times have an urge to do something harmful or shocking?

35. Have you sometimes sensed an evil presence around you, even though you could not see it?
36. Have you ever thought that you had special, almost magical powers?
37. Do you ever have the urge to break or smash things?
38. Do you dread going into a room by yourself where other people have already gathered and are talking?
39. Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?
40. Are there very few things that you have ever enjoyed doing?
41. Do you often have difficulties in controlling your thoughts?
42. When you look in the mirror does your face sometimes seem quite different from usual?
43. Do you feel very close to your friends?